Practice parameter

Disease management of atopic dermatitis: an updated practice parameter

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TABLE OF CONTENTS

PREFACE

Atopic dermatitis is an important component of the atopic diathesis. It not only frequently accompanies allergic respiratory disease but often is the first manifestation of allergic disease. Most patients with atopic dermatitis will develop allergic rhinitis or asthma. The evaluation and management of atopic dermatitis are, therefore, an integral part of an allergist/immunologist's training and practice. It is also important for the primary care physician to understand the basis for effective evaluation and management of patients with this condition, since atopic dermatitis affects more than 10% of children and can have a significant impact on the patient's quality of life. As discussed in this document, it is also important for the primary care physician to know when to appropriately consult a specialist in atopic dermatitis.

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Since the initial Parameter on Atopic Dermatitis was published in 1997, there have been remarkable advances in the understanding of the pathophysiology of atopic dermatitis.[1] The pathogenesis of atopic dermatitis involves a complex inflammatory process, our understanding of which is constantly undergoing revision, as more data become available on the role of IgE-bearing Langerhans cells, atopic keratinocytes, monocytes/macrophages, eosinophils, and mast cells and their interaction with interleukin 4 (IL-4), IL-5, and IL-13 producing T_H2 lymphocytes. There is a complicated interaction between these cells and their products and susceptibility genes and the host environment, which leads to the clinical findings that characterize atopic dermatitis.

The major objective of the parameter, *Disease Management of Atopic Dermatitis: An Updated Practice Parameter*, is to improve the care of patients with atopic dermatitis. This should be accomplished by establishing boundaries for the evaluation and management of patients with this condition while reducing unwanted and unnecessary variations in treatment.

This updated Parameter on Atopic Dermatitis was developed by the Joint Task Force on Practice Parameters, which has published 11 practice parameters for the field of allergy/immunology, including the original Parameter on Atopic Dermatitis. The 3 national allergy and immunology societies, the American College of Allergy, Asthma and Immunology (ACAAI), the American Academy of Allergy, Asthma, and Immunology (AAAAI), and the Joint Council of Allergy, Asthma and Immunology (JCAAI), have given the Task Force the responsibility for updating existing parameters. This document builds on the original Parameter on Atopic Dermatitis. It was written and reviewed by subspecialists in allergy and immunology and was funded by the 3 allergy and immunology organizations noted above.

Donald Y. M. Leung, MD, PhD, who chaired the workgroup that developed the original Parameter on Atopic Dermatitis, prepared the initial draft of the updated parameter on this condition. The Joint Task Force revised the initial draft into a working draft of the document, which included a review of the medical literature using a variety of search engines such as PubMed. Published clinical studies were rated by category of evidence and used to establish the strength of a clinical recommendation (Table 1). The working draft of the updated Parameter on Atopic Dermatitis was then reviewed by a number of experts in allergy and immunology and specifically by experts on atopic dermatitis. This document, therefore, represents an evidence-based, broadly accepted consensus opinion.

The updated Parameter on Atopic Dermatitis contains an annotated algorithm that presents the major decision points for the appropriate evaluation and management of atopic dermatitis (Fig 1). Also included in this parameter are summary statements, which represent the key points in the evaluation and management of atopic dermatitis. These summary statements appear again before each section in this document, followed by text that supports the summary statement(s). There are sections on Definitions, Immunopathology, Clinical Diagnosis, First-line Management and Treatment, Identification and Elimination of Triggering Factors, Microbes, Emotional Stress, Patient Education, and Treatment of the Difficult-to-Manage Patient.

Table 1. Classification of Evidence and Recommendations*

Category of evidence	
Ia	Evidence from meta-analysis of randomized controlled trials
Ib	Evidence from at least 1 randomized controlled trial
IIa	Evidence from at least 1 controlled study without randomization
IIb	Evidence from at least 1 other type of quasi-experimental study
III	Evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies, and case-control studies
IV	Evidence from expert committee reports or opinions or clinical experience of respected authorities or both
LB	Evidence from laboratory-based studies†
Strength of recommendation	
A	Directly based on category I evidence
B	Directly based on category II evidence or extrapolated from category I evidence
C	Directly based on category III evidence or extrapolated from category I or II evidence
D	Directly based on category IV evidence or extrapolated from category I, II, or III evidence
E	Directly based on category LB evidence†
F	Based on consensus of the Joint Task Force on Practice Parameters†

*Data are from Shekelle PG, Woolf SH, Eccles M, Grimshaw J. Clinical guidelines: developing guidelines. *BMJ.* 1999;318:593–596.
† Added by current authors.

There are a number of legitimate reasons for the development of practice parameters that affect the interaction with managed care and health care providers; education of medical students, interns, residents, and fellows; and the establishment of boundaries and support for the practicing physician. The primary reason for developing practice parameters, however, must always be to improve the quality of care for the patient. If used appropriately, this updated Parameter on Disease Management of Atopic Dermatitis will be another step toward achieving that goal.

EXECUTIVE SUMMARY

Atopic dermatitis is a genetically transmitted, chronic inflammatory skin disease that affects 10% to 20% of children and 1% to 3% of adults.[1] The vast majority of patients develop the disease before the age of 5 years, although it can also present in adulthood.[2] Atopic dermatitis is the first manifestation of atopy in many patients who later develop allergic rhinitis and/or asthma,[3] a pattern that has been referred to epidemiologically as "the atopic march." Pruritus, scratching, and chronic and/or relapsing eczematous lesions are major hallmarks of the disease. In infants and young children, there is a characteristic pattern of involvement of the face, neck, and extensor skin surfaces. In older children and adults, the skin lesions often involve lichenification and are usually localized to the flexural folds of the extremities. Factors that may

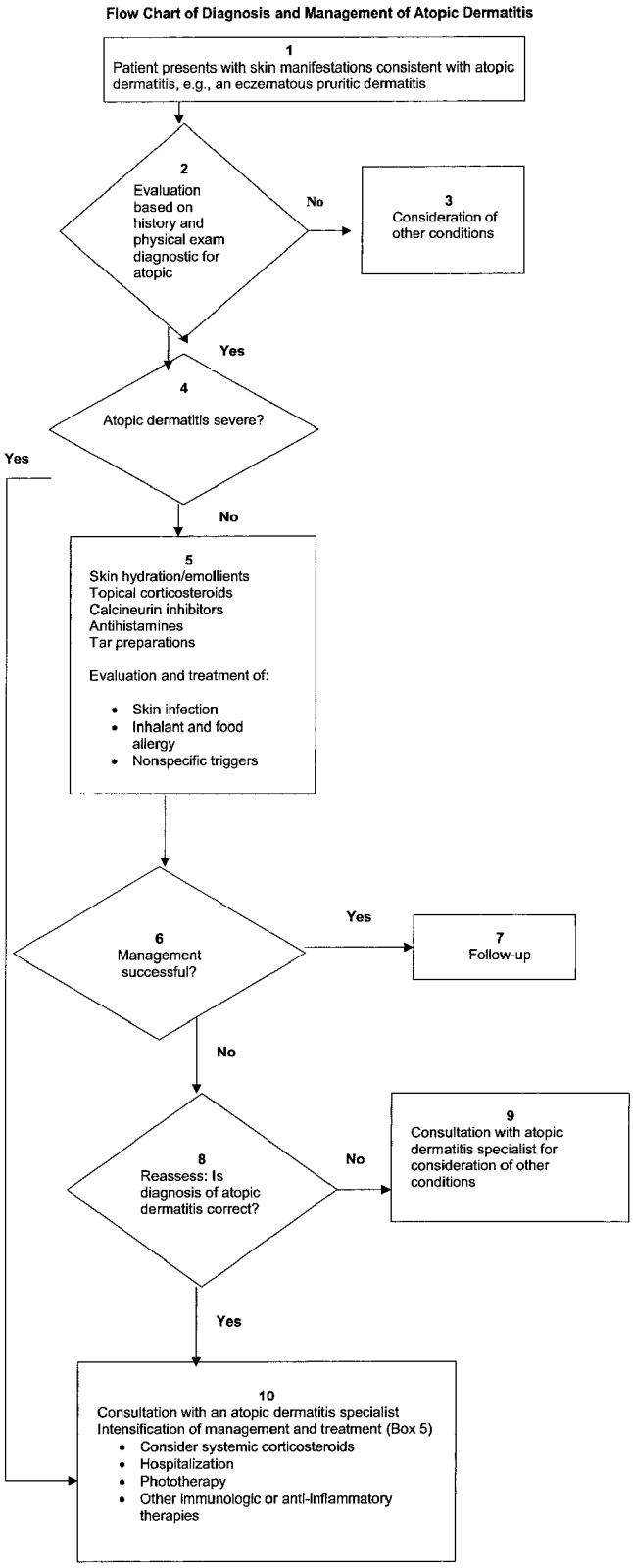

Figure 1. Flow chart of diagnosis and management of atopic dermatitis.

exacerbate symptoms in atopic dermatitis patients include temperature, humidity, irritants, infections, food, inhalant and contact allergens, and emotional stress.[4] Food allergy has been implicated in approximately one third of children with atopic dermatitis, although specific IgE is often present without clear relevance to the disease process.[5]

The pathogenesis of atopic dermatitis involves a complex interaction between genetic and environmental factors. Xerosis, scratching, and both colonization[2,6–8] and infection[9] of the skin by *Staphylococcus aureus* all contribute to the disease process. As with allergic rhinitis and asthma, the inflammatory reaction in atopic dermatitis involves T_H2 lymphocyte activation, resulting in the production of IL-4, IL-5, and IL-13.[2] Other cells involved in this inflammation include IgE-bearing Langerhans cells, atopic keratinocytes, lymphocytes, monocytes/macrophages, eosinophils, and mast cells.[10–12]

The diagnosis of atopic dermatitis is based on its clinical presentation rather than diagnostic testing.[13] However, the judicious use of percutaneous skin tests or in vitro testing for the presence of specific IgE to relevant allergens is a sensitive way of identifying potential allergic triggering factors. Double-blind food challenges are sometimes necessary to determine the relevance of specific food ingestion to symptoms.[14]

The effective management of atopic dermatitis involves some combination of trigger avoidance,[14–16] measures to restore skin barrier function, and anti-inflammatory medication.[4] Trigger avoidance should be individualized based on a careful history and the results of specific IgE testing. Barrier function can be improved by careful hydration and emollient application, such as soaking in a lukewarm bath for 20 to 30 minutes followed by the immediate application of an emollient.[17]

There are multiple anti-inflammatory medication options available for treating atopic dermatitis. Topical corticosteroids are appropriate for the vast majority of patients, and the potency of the corticosteroid agent chosen should be individualized based on the severity of the dermatitis, the location of the affected skin, the surface area of the affected skin, and the age of the patient.[4] Clinical exacerbations may require temporarily switching to a more potent topical agent or using a tapering course of a systemic corticosteroid. Tacrolimus and pimecrolimus are anti-inflammatory calcineurin inhibitors and alternatives to corticosteroids that have been recently approved for topical use in adults and children with atopic dermatitis.[18–21] These agents interrupt activation of lymphocytes and other inflammatory cells,[18,22] and to date they have been very well tolerated.[23–26]

There are a variety of other treatment options for patients with severe or refractory atopic dermatitis. These include wet dressings and occlusion,[27,28] phototherapy,[29] systemically administered immunosuppressants such as cyclosporin[27] or interferon gamma,[30] and antimetabolites.[31,32] In rare cases, short-term hospitalization is a useful way to temporarily reduce exposure to environmental and emotional triggers while initiating intensive patient education, diagnostic testing

(such as skin testing and food challenges), and aggressive medical treatment.

ANNOTATIONS TO FIGURE 1

Annotation 1: Patient Presents with Skin Manifestations Consistent with Atopic Dermatitis (eg, an Eczematous Pruritic Dermatitis)

There is no objective laboratory test for the diagnosis of atopic dermatitis. Therefore, the diagnosis of atopic dermatitis is based on a constellation of clinical features. These include (1) the essential feature, which is a pruritic dermatitis; (2) typical features, such as facial and extensor eczema in infants and children, flexural eczema in adults, and chronic or relapsing dermatitis; (3) frequently associated features, such as personal or family history of atopic disease, xerosis, cutaneous infections, nonspecific dermatitis of the hands or feet, elevated serum IgE levels, frequent occurrence of nonspecific decrease in cell-mediated immune response (anergy), positive immediate-type allergy skin tests and early age of onset; and (4) other features, such as white dermatographism and delayed blanch response, anterior subcapsular cataracts, keratoconus, Dennie-Morgan infraorbital folds, orbital darkening, facial erythema, or pallor.

Annotation 2: Evaluation Based on History and Physical Examination Diagnostic for Atopic Dermatitis?

Atopic dermatitis often is associated with an early age of onset, with approximately 80% of cases starting before the age of 5 years. It frequently is associated with respiratory allergy and a number of other features, such as Dennie-Morgan infraorbital folds, white dermatographism, and facial pallor.

Acute and subacute lesions of atopic dermatitis are characterized by intensely pruritic, erythematous papulovesicles associated with excoriation and serous exudate. Lesions that do not appear papulovesicular clinically must demonstrate spongiosis histologically. Chronic atopic dermatitis is characterized by lichenification, papules, and excoriations. At all stages of atopic dermatitis, patients usually have dry skin. The distribution and skin reaction pattern vary according to the patient's age and disease activity. The skin distribution pattern in infants and young children generally involves the face, neck, and extensor skin surfaces. In contrast, in older children and adults who have long-standing skin disease, lichenification and localization of the rash to the flexural folds of the extremities usually are found. Chronic hand (and/or foot) eczema may be the primary or sole manifestation of many atopic adults.

Annotation 3: Consideration of Other Conditions

A firm diagnosis of atopic dermatitis depends on the exclusion of other skin conditions with similar symptoms and signs. Failure of any response to "standardized" management of atopic dermatitis is a reason to consider other eczematous conditions. Skin conditions that may mimic atopic dermatitis fall into the following categories: (1) chronic dermatoses, such as seborrheic and contact dermatitis, nummular eczema, psoriasis, and ichthyoses; (2) infections and infestations such as scabies, human immunodeficiency virus, and dermophytosis; (3) malignancies, such as cutaneous T-cell lymphoma and Letterer-Siwe disease; (4) immunologic disorders, such as dermatitis herpetiformis, graft-vs-host disease, and dermatomyositis; (5) immunodeficiencies, such as Wiskott-Aldrich, severe combined immunodeficiency disease, hyper-IgE, and DiGeorge syndrome; and (6) metabolic disorders, such as zinc, pyridoxine, or niacin deficiency and phenylketonuria. In situations in which the diagnosis is not obvious, a skin biopsy should be considered. The skin biopsy should be performed by a physician trained and experienced in performing the procedure and should be interpreted by a qualified dermatopathologist.

Annotation 4: Is the Atopic Dermatitis Severe?

Severe atopic dermatitis is characterized by intensely pruritic, widespread skin lesions that often are complicated by persistent bacterial, viral, or fungal infections. The presence of keratoconus, keratoconjunctivitis, anterior cataracts, and eczema vaccinatum suggests that the atopic dermatitis is particularly severe, which may be related to chronicity.

The extent and severity of atopic dermatitis can be determined by careful examination of the patient's skin, grading the extent of affected areas (eg, percentage of involvement of the head, upper limbs, trunk, and lower limbs), and defining the severity of the following signs of eczema: induration, erythema, excoriation, lichenification, scaling, oozing, weeping, and crusting. In general, patients who have more than 20% skin involvement (or 10% of skin involvement if affected areas include the eyelids, hands, or intertriginous areas) that has not been responsive to first-line treatment should be considered for consultation with a specialist. Other patients who should be considered as having severe atopic dermatitis include:

- Patients with extensive skin involvement who are at risk for exfoliation.
- Patients who require ongoing or frequent treatment with high-potency topical glucocorticoids or systemic glucocorticoids.
- Patients who require hospitalization for severe eczema or skin infections related to the atopic dermatitis.
- Patients with ocular or infectious complications.
- Patients who have significant disruption of their quality of life (eg, sleepless nights, school or work days lost, etc).
- Patients who are generally erythrodermic.

Patients not previously receiving appropriate treatment for atopic dermatitis should be started on first-line therapy, and attempts should be made to identify potential triggers.

Annotation 5: Management of Atopic Dermatitis

The treatment of atopic dermatitis is directed at symptom relief and reduction of cutaneous inflammation. Characterization of each patient's skin disease severity and the reduction of exacerbating factors are critical for effective management. All patients require skin hydration in combination with

an effective emollient. Potential trigger factors should be identified and eliminated. These include irritants, allergens, and emotional stresses. Therapy must be individualized and is dependent on whether the patient is experiencing an acute flare or dealing with the management of chronic atopic dermatitis.

The severity of atopic dermatitis is based on the extent of skin involvement, the intensity of pruritus, the presence of complications, the effect on quality of life, and the amount of medication required for control.

The initial management of atopic dermatitis may consist of the following categories of treatment: hydration, topical corticosteroids, topical calcineurin inhibitors, tar preparations, and antihistamines.

Tacrolimus, a calcineurin inhibitor, has been shown to be effective and safe for use in atopic dermatitis. Most patients experience a dramatic reduction of pruritus within 3 days of initiating treatment, as well as significant improvement in quality of life. Pimecrolimus also has been shown to be effective and safe for the treatment of atopic dermatitis. When used as long-term maintenance therapy, topical preparations of this drug reduce the number of flares of atopic dermatitis and the requirement for corticosteroid treatment.

There are many factors that may contribute to exacerbations of atopic dermatitis, including food allergens, aeroallergens, infections, temperature, humidity, irritants, and emotional stress.

Skin testing or in vitro testing for IgE antibodies can be useful in the identification of potential allergens. In particular, negative skin tests or in vitro tests can be used to exclude allergic trigger factors as a cause of atopic dermatitis. Positive skin test results or in vitro test results do not prove that a particular allergen causes clinical symptoms, but they may guide the clinician in considering possible causes. This is particularly true in the case of foods, where controlled food challenges or elimination diets may be needed to confirm or exclude clinical sensitivity to foods.

Skin infections should be treated with short courses of appropriate antimicrobial therapy, with an emphasis on appropriate treatment for staphylococcal infections. Herpetic and dermatophytic infections also need to be considered and treated after appropriate diagnosis has been confirmed.

Annotation 6: Is the Management Successful?

Response to therapy may be classified as a complete response, a partial response, or a treatment failure. Complete response and eradication of the patient's eczema, in the short term, is unusual unless there is a clear-cut trigger (eg, a food allergen that could be eliminated). Atopic dermatitis is a chronic relapsing skin condition, and therefore most patients will have a partial response with reduction in pruritus and the extent of skin disease. These patients will need long-term follow-up for adjustment of medications according to the severity of the illness. Patients who do not respond to treatment should be completely reassessed to be certain of the diagnosis, and alternative treatment should be considered.

Annotation 7: Follow-up

To achieve effective control of a patient's atopic dermatitis, it is important to educate patients and family members about the chronic nature of their disease, exacerbating factors, and appropriate treatment options. This is important to ensure cooperation and compliance with the treatment plan. Written information that includes detailed skin care recommendations, environmental control, and general information about the disease should be provided. Patients should be educated on how to monitor their disease and know how to respond to changes in their status and when to seek additional medical help. The treatment plan should be reviewed during follow-up visits, and the patient and/or parent should demonstrate an appropriate level of understanding to ensure a good outcome. Adequate time and teaching materials are necessary to provide effective education. Patient support organizations that provide updates on progress in atopic dermatitis research are important resources for these patients. Follow-up of patients with atopic dermatitis also should include evaluation for potential triggers of exacerbations (eg, aeroallergens, infection, emotional factors) and cooperative management with the patient and/or parent to prevent such exacerbations.

Annotation 8: Reassess: Is Diagnosis of Atopic Dermatitis Correct?

In patients who do not achieve the goals of atopic dermatitis management, it is important to reassess whether the diagnosis is correct. With the lack of a characteristic skin lesion or a confirmatory laboratory test result, the diagnosis depends on clinical symptoms and the physical examination. Concomitant allergic rhinitis and/or asthma increase the likelihood that the diagnosis of atopic dermatitis is correct. As discussed in annotation 1, many skin conditions may masquerade as atopic dermatitis.

When reassessing patients, it is helpful to consider the following points. Most patients who present with atopic dermatitis are younger than 5 years but are infrequently younger than 6 weeks. Any infant with an eczematous rash presenting earlier than the first month of life should be carefully evaluated for the presence of congenital immunodeficiency, particularly if the course is complicated by recurrent infections and failure to thrive. Atopic dermatitis does not usually affect the diaper area or the nose exclusively. Differentiation of seborrheic dermatitis from atopic dermatitis may be difficult in infants. It is important to consider contact dermatitis and skin infections as complicating factors.

Annotation 9: Consultation with an Atopic Dermatitis Specialist for Consideration of Other Conditions

Patients who are refractory to first-line therapy and who have severe atopic dermatitis with significant dysfunction should have a consultation with an atopic dermatitis specialist, such as an allergist or dermatologist. Such consultation is recommended when the diagnosis of atopic dermatitis is in doubt and for identification of potential allergen triggers, patient education, and implementation of alternative therapies, including potent anti-inflammatory and immunomodulatory agents.

Cooperation between the patient and/or the patient's guardian(s), the primary care physician, and the allergist or dermatologist is important in the implementation of strategies necessary for the care of patients with chronic atopic dermatitis. Even when an atopic dermatitis specialist is consulted, the primary care physician continues to play an important role in the care of patients with atopic dermatitis by ensuring continuity of care.

Annotation 10: Consultation with an Atopic Dermatitis Specialist: Intensification of Management and Treatment

When atopic dermatitis is either severe or has not responded to appropriate first-line management strategies, specialist consultation should be obtained. This allows both a reevaluation of first-line treatment approaches (eg, hydration, emollients, topical corticosteroids, pimecrolimus, tacrolimus, and tar preparations) and consideration of alternative therapy. Examples of alternative strategies include (1) the application of wet dressings in combination with topical corticosteroids; (2) short-term treatment with systemic corticosteroids with appropriate tapering to avoid rebound; (3) phototherapy with ultraviolet light (UV-B or UV-A [PUVA]); (4) immunomodulatory or immunosuppressive agents; (5) hospitalization to separate the patient from environmental allergens while administering other therapies; and (6) allergen immunotherapy when aeroallergens are clearly implicated in dermatitis flares. In light of potential adverse effects, a careful risk-benefit analysis should be undertaken before initiating any of these alternative therapies. For patients who do not respond to these approaches, investigational treatment can be considered.

SUMMARY STATEMENTS

Definitions

Summary statement 1. Atopic dermatitis is a familial, chronic inflammatory skin disease that commonly presents during early infancy and childhood but can persist or start in adulthood. (C)

Immunopathology

Summary statement 2. Most individuals with atopic dermatitis have elevated serum IgE levels, which are often very high. (C)

Summary statement 3. Pathogenesis of atopic dermatitis involves a complex inflammatory process associated with IgE-bearing Langerhans cells, atopic keratinocytes, lymphocytes, monocytes/macrophages, eosinophils, and mast cells. (C)

Summary statement 4. There is an increased frequency of T_H2 cells producing IL-4, IL-5, and IL-13, but little interferon-γ has been found in the peripheral blood and acute skin lesions of patients with atopic dermatitis. The clinical manifestations of atopic dermatitis result in large part from stimulation of the T_H2 wing of the immunologic pathways. (C)

Summary statement 5. There is a complex interaction among susceptibility genes, the host environment, and multiple immunologic cells, leading to acute and chronic lesions that characterize this skin disease. (B)

Clinical Diagnosis

Summary statement 6. There is no objective diagnostic test for the clinical confirmation of atopic dermatitis. (D)

Summary statement 7. The diagnosis of atopic dermatitis is based on a constellation of clinical features. (D)

Summary statement 8. Pruritus and chronic or relapsing eczematous lesions with typical morphology and distribution in patients with a history of atopy are essential for diagnosis. (F)

Summary statement 9. Acute and subacute skin lesions are most often seen in infants and young children and are characterized by intensely pruritic erythematous papulovesicular lesions associated with excoriation and serous exudate. (D)

Summary statement 10. Chronic atopic dermatitis is characterized by lichenification, papules, and excoriations. (D)

First-line Management and Treatment

Summary statement 11. The intensity of management and treatment of atopic dermatitis is dictated by the severity of illness, which relates to the effect of atopic dermatitis on the quality of life of the patient and his or her family. (A)

Summary statement 12. Successful management requires a systematic, multipronged approach that includes antipruritic therapy, skin hydration, topical anti-inflammatory medications, and the identification and possible elimination of exacerbating factors. (A)

Skin Hydration

Summary statement 13. Atopic dermatitis is characterized by reduced skin barrier function due to loss of vital lipids, which leads to enhanced water loss and dry skin. (E)

Summary statement 14. Moisturizers such as lukewarm soaking baths for at least 20 minutes followed by the application of an occlusive emollient to retain moisture can give the patient symptomatic relief. (D)

Summary statement 15. Emollients, available in the form of lotions, creams, and ointments, should be used as first-line therapy. (D)

Topical Corticosteroids

Summary statement 16. Topical corticosteroids, applied to areas of eczema, are effective treatment for atopic dermatitis. (A)

Summary statement 17. Low-potency corticosteroids are recommended for maintenance therapy, whereas intermediate- and high-potency corticosteroids should be used for the treatment of clinical exacerbation and applied to affected areas of skin over short periods of time. (A)

Summary statement 18. Potent fluorinated corticosteroids should be avoided on the face, the eyelids, the genitalia, and the intertriginous areas, as well as in young infants. (D)

Summary statement 19. Ultrahigh-potency corticosteroids should be used only for very short periods of time (several days) and only in areas that are lichenified. (D)

Summary statement 20. The degree of corticosteroid absorption through the skin, and hence the potential for systemic adverse effects, is directly dependent on the surface

area of the skin involved, the use of occlusive dressing, and the potency of the corticosteroid preparation. (D)

Topical Calcineurin Inhibitors

Tacrolimus

Summary statement 21. Tacrolimus ointment has been shown to be effective and safe in both adults and children for the treatment of mild-to-moderately severe atopic dermatitis, with most patients experiencing a reduction of pruritus within 3 days of initiating therapy. (A)

Summary statement 22. Tacrolimus ointment applied on up to 100% of the body surface in adults and children has demonstrated sustained efficacy with no significant systemic adverse effects. (A)

Summary statement 23. A local burning sensation is the most common adverse effect associated with tacrolimus. This may limit its usefulness in certain patients. (A)

Summary statement 24. Tacrolimus ointment can be used safely for facial and eyelid eczema. (D)

Pimecrolimus

Summary statement 25. Topical pimecrolimus cream is a calcineurin inhibitor that decreases the number of flares of atopic dermatitis, reduces the need for corticosteroids, and controls pruritus. (A)

Tar Preparations

Summary statement 26. Although tar preparations are widely used in the treatment of atopic dermatitis, there are no randomized, controlled studies that have demonstrated their efficacy. (A)

Summary statement 27. Newer coal tar products have been developed that are more cosmetically acceptable, with respect to odor and staining of clothes, than some older products. (B)

Summary statement 28. Tar preparations should not be used on acutely inflamed skin, since this may result in additional skin irritation. (D)

Antihistamines

Summary statement 29. Some patients may benefit from the use of antihistamines for the relief of pruritus associated with atopic dermatitis. (C)

Summary statement 30. Treatment of atopic dermatitis with topical antihistamines is generally not recommended because of potential cutaneous sensitization. (C)

Identification and Elimination of Triggering Factors

Summary statement 31. Avoidance of common irritants (eg, soaps, toiletries, wool, chemicals) that trigger the itch-scratch cycle is recommended. (B)

Summary statement 32. Control of temperature and humidity may be useful for preventing pruritus. (D)

Summary statement 33. Aeroallergens such as house dust mites, animal allergens, and pollens may cause exacerbation, and therefore exposure to them should be minimized. (A)

Summary statement 34. Possible allergenic triggers of atopic dermatitis can be confirmed by skin tests and in vitro tests for specific IgE antibodies and in some cases by patch tests that may produce immediate or delayed reactions to protein allergens. (B)

Summary statement 35. Food allergens trigger atopic dermatitis more commonly in young infants and children than in adults. (D)

Microbes

Summary statement 36. Patients with moderate-to-severe atopic dermatitis have been found to make IgE antibodies against staphylococcal toxins present on their skin. (B)

Summary statement 37. A course of an appropriate systemic antibiotic should be considered in patients who are heavily colonized or infected with staphylococcal *aureus*. Antibiotic treatment maybe more difficult if staphylococcal *aureus* is resistant. (D)

Summary statement 38. Atopic dermatitis can be complicated by recurrent viral skin infections, such as herpes simplex, warts, and molluscum contagiosum. (D)

Summary statement 39. Smallpox vaccination or even exposure of patients with atopic dermatitis to recently vaccinated individuals may cause a severe, widespread, potentially fatal dermatitis called *eczema vaccinatum*, which is similar in appearance to eczema herpeticum. (C)

Summary statement 40. Dermatophytic infections can complicate atopic dermatitis and may contribute to exacerbation (D) of disease activity. (LB)

Emotional Stress

Summary statement 41. Emotional factors do not cause atopic dermatitis but often cause exacerbation and have been found to induce immune activation as well as increase pruritus and scratching. (D)

Patient Education

Summary statement 42. To achieve effective control of atopic dermatitis, it is important to educate patients and family members about the chronic nature of atopic dermatitis, exacerbating factors, and appropriate treatment options, including patient support organizations to enhance adherence. (B)

Treatment of the Difficult-to-Manage Patient

Wet dressing and occlusion

Summary statement 43. Wet dressings may serve as an effective barrier against persistent scratching, allowing more rapid healing of excoriated lesions. (B)

Summary statement 44. Application of wet-wrap dressings in combination with topical corticosteroids can be efficacious in the treatment of refractory atopic dermatitis. (A)

Allergen immunotherapy

Summary statement 45. Although the effectiveness of allergen immunotherapy in the treatment of atopic dermatitis has not been conclusively demonstrated, there are selected patients with atopic dermatitis who may benefit from such treatment. (F)

Systemic corticosteroids

Summary statement 46. The use of systemic corticosteroids may be required in the treatment of severe, recalcitrant chronic atopic dermatitis. (F)

Summary statement 47. The dramatic clinical improvement that may occur after administration of systemic corticosteroids may be associated with an equally dramatic rebound flaring of atopic dermatitis following discontinuation of systemic corticosteroids. (D)

Phototherapy

Summary statement 48. Natural sunlight can be beneficial for atopic dermatitis, but sunburn and overheating should be avoided. (A)

Summary statement 49. Ultraviolet therapy can be a useful adjunct in the treatment of recalcitrant atopic dermatitis. (D)

Summary statement 50. Phototherapy with PUVA should be restricted to patients with recalcitrant atopic dermatitis. (B)

Systemic immunomodulating agents

Summary statement 51. Immunosuppressive agents such as cyclosporin, interferon gamma, mycophenolate mofetil, and azathioprine have been shown to provide benefit for certain cases of severe refractory atopic dermatitis, but potential benefits should be weighed against their potentially serious adverse effects. (F)

Hospitalization

Summary statement 52. Hospitalization can result in an improvement in atopic dermatitis by removing the patient from environmental allergens and irritants and by providing patient education and improving compliance. (D)

Investigative approaches

Summary statement 53. There are certain investigative treatments that have been proposed for the management of atopic dermatitis. These remain unproven at this time. (D)

Consultation with an atopic dermatitis specialist

Summary statement 54. Patients refractory to first-line therapy should be evaluated by an atopic dermatitis specialist. (F)

DEFINITIONS

Summary statement 1. Atopic dermatitis is a familial, chronic inflammatory skin disease that commonly presents during early infancy and childhood but can persist or start in adulthood. (C)

Atopic dermatitis is a familially transmitted, chronic inflammatory skin disease that commonly presents during early infancy and childhood but can persist or start in adulthood.[2] It often presents as the first step in the atopic march toward respiratory allergy. Recent interest in atopic dermatitis has been sparked by reports of its increasing prevalence and the significant adverse impact it can have on quality of life. Atopic dermatitis is a major public health problem worldwide, with a lifetime prevalence in children of 10% to 20%.[1] The prevalence of atopic dermatitis in adults is approximately 1% to 3%. Wide variations in prevalence have been observed within countries inhabited by similar ethnic groups, suggesting that environmental factors determine atopic dermatitis expression.[33]

IMMUNOPATHOLOGY

Summary statement 2. Most individuals with atopic dermatitis have elevated serum IgE levels, which are sometimes extremely high. (C)

Summary statement 3. Pathogenesis of atopic dermatitis involves a complex inflammatory process associated with IgE-bearing Langerhans cells, atopic keratinocytes, lymphocytes, monocytes/macrophages, eosinophils, and mast cells. (C)

Summary statement 4. There is an increased frequency of T_H2 cells producing IL-4, IL-5, and IL-13, but little interferon-γ has been found in the peripheral blood and acute skin lesions of patients with atopic dermatitis. The clinical manifestations of atopic dermatitis result in large part from stimulation of the T_H2 wing of the immunologic pathways. (C)

Summary statement 5. There is a complex interaction between susceptibility genes, the host environment, and multiple immunologic cells, leading to acute and chronic lesions that characterize this skin disease. (B)

Since the initial Joint Task Force Practice Parameters on Atopic Dermatitis was published,[34] there have been remarkable advances in our understanding of the pathophysiology of atopic dermatitis. Nearly 80% of patients with atopic dermatitis develop allergic rhinitis or asthma. In such patients, atopic dermatitis may be considered the skin manifestation of a systemic allergic response.[3] An increased frequency of T_H2 cells producing IL-4, IL-5, and IL-13 but little interferon-γ has been found in the peripheral blood and acute skin lesions of patients with atopic dermatitis.[10] This likely contributes to the increased eosinophilia and IgE sensitization to factors in the host environment that characterize most patients with atopic dermatitis. The development of T_H2 cells in atopic dermatitis is related to several factors, including (1) the cytokine microenvironment in which T-cell development takes place; (2) allergic mediators; (3) the costimulatory signals used during T-cell activation; and (4) the antigen-presenting cell.[35–40] There has been considerable interest in the unique features of IgE-bearing Langerhans cells and atopic keratinocytes in promoting the skin lesions of atopic dermatitis.[11,12]

The picture that has emerged of the pathogenesis of atopic dermatitis involves a complex interaction between susceptibility genes, the host environment, and multiple immunologic cells, resulting in the acute and chronic skin lesions that characterize this skin disease. Effective therapy requires a multipronged approach to reduce environmental triggers and skin inflammation and restore skin barrier function.

CLINICAL DIAGNOSIS

Summary statement 6. There is no objective diagnostic test for the clinical confirmation of atopic dermatitis. (D)

Summary statement 7. The diagnosis of atopic dermatitis is based on a constellation of clinical features. (D)

Summary statement 8. Pruritus and chronic or relapsing eczematous lesions with typical morphology and distribution in patients with a history of atopy are essential for diagnosis. (F)

Summary statement 9. Acute and subacute skin lesions are most often seen in infants and young children and are characterized by intensely pruritic erythematous papulovesicular lesions associated with excoriation and serous exudate. (D)

Summary statement 10. Chronic atopic dermatitis is characterized by lichenification, papules, and excoriations. (D)

At the initial encounter with any patient seeking treatment for atopic dermatitis, particularly if poorly controlled, it is essential to confirm that the correct diagnosis has been made. There is no objective diagnostic test for the clinical confirmation of atopic dermatitis. Therefore, the diagnosis of atopic dermatitis is based on the constellation of clinical features.[13] Of the major features, pruritus and chronic or relapsing eczematous lesions with typical morphology and distribution are essential for diagnosis. Although pruritus may occur throughout the day, it is usually worse in the early evening and night. Its consequences are scratching followed by the elicitation of eczematous skin lesions.

Acute and subacute skin lesions are characterized by intensely pruritic, erythematous papulovesicles associated with excoriation, and serous exudate. Chronic atopic dermatitis is characterized by lichenification, papules, and excoriations. Patients usually have dry, pale, pasty skin. The distribution and skin reaction pattern vary according to the patient's age, disease activity, and accessibility to scratching. In infants and young children, the rash generally involves the face, neck, and extensor skin surfaces. In older children and adults who have long-standing skin disease, lichenification and localization of the rash to the flexural folds of the extremities are common. Chronic hand eczema may be the primary manifestation in many adults with a history of atopic dermatitis.

Atopic dermatitis is often associated with an early age of onset, with most cases starting before the age of 5 years. Atopic dermatitis can be triggered by IgE-mediated events in many patients, but it can be triggered in some patients by non–IgE-mediated events.[2,41] Therefore, although respiratory allergy is an important associated condition in patients with atopic dermatitis, it is not essential for diagnosis of this condition. Although a number of other features, such as Dennie-Morgan infraorbital folds, white dermatographism, or facial pallor, can be seen, they are too nonspecific for use in making a diagnosis of atopic dermatitis. A firm diagnosis of atopic dermatitis depends on the exclusion of other skin conditions that share symptoms and signs.

FIRST-LINE MANAGEMENT AND TREATMENT

Summary statement 11. The intensity of management and treatment of atopic dermatitis is dictated by the severity of illness, which relates to the effect of atopic dermatitis on the quality of life of the patient and his or her family. (A)

Summary statement 12. Successful management requires a systematic, multipronged approach that includes antipruritic therapy, skin hydration, topical anti-inflammatory medications, and the identification and possible elimination of exacerbating factors. (A)

The intensity of management and treatment is dictated by the severity of illness and its effect on the patient and immediate family. Successful management requires a systematic, multipronged approach that includes skin hydration, topical anti-inflammatory medications, and the identification and possible elimination of exacerbating factors, including irritants, allergens, emotional stressors, and infectious agents.[4] Scratching plays an important role in the development of cutaneous lesions in atopic dermatitis. Control of pruritus is, therefore, an important part of treatment, recognizing that patients may be exposed to both exogenous (eg, humidity, allergens) and endogenous (eg, stress) provocation factors. Dry skin in the winter months damages the stratum corneum barrier, causing an increased susceptibility to irritants and increased itching, whereas sweating in the warm humid months of the summer may also trigger itching. Patients with atopic dermatitis frequently will experience an accentuation of their itching during times of stress and/or exposure to specific allergens. Many factors may lead to an intensification of pruritus, and treatment plans should be individualized to address trigger factors that are unique to the individual patient.

Skin Hydration

Summary statement 13. Atopic dermatitis is characterized by reduced skin barrier function due to loss of vital lipids, which leads to enhanced water loss and dry skin. (E)

Summary statement 14. Moisturizers such as lukewarm soaking baths for at least 20 minutes followed by the application of an occlusive emollient to retain moisture can give the patient symptomatic relief. (D)

Summary statement 15. Emollients, available in the form of lotions, creams, and ointments, should be used as first-line therapy. (D)

Atopic dermatitis is characterized by reduced skin barrier function. This is likely due, at least in part, to high expression of sphingomyelin deacylase, which decreases ceramide levels in atopic dermatitis skin.[42,43] The loss of vital skin lipids results in enhanced transepidermal water loss and dry skin (xerosis). Application of ceramide-rich lipids may improve skin barrier function and reduce the severity of atopic dermatitis.[44] Xerosis contributes to the development of epithelial microfissures and cracks, which favor the entry of skin microbes and allergens. This problem usually becomes exacerbated during the dry winter months and aggravated in certain work environments. Lukewarm soaking baths for at least 20 minutes followed by the application of an occlusive emollient to retain moisture can give the patient excellent symptomatic relief. Addition of substances such as oatmeal or baking soda to the bath water may have a soothing antipruritic effect for certain patients but does nothing to increase water absorption. Emollients make a major contribution to controlling the pru-

ritus of atopic dermatitis, while maintaining a soft texture to the skin.[45] They offer a particular advantage when applied immediately after bathing to maintain hydration of the epidermis.

Emollients are available in the form of lotions, creams, and ointments. Lotions and creams may be irritating due to preservatives, solubilizers, and fragrances. Lotions also contain water and may be drying due to an evaporative effect. Hydrophilic ointments can be obtained in varying degrees of viscosity. Some patients prefer a thicker preparation than others might require. Occlusive ointments are sometimes not well tolerated because of interference with the function of the eccrine sweat ducts and may induce the development of a sweat retention dermatitis. In these patients, less occlusive agents should be used. An increased incidence of peanut allergy has been reported in children in the United Kingdom using emollients with refined peanut oil for atopic dermatitis.[45]

Topical Corticosteroids

Summary statement 16. Topical corticosteroids, applied to areas of eczema, are effective treatment for atopic dermatitis. (A)

Summary statement 17. Low-potency corticosteroids are recommended for maintenance therapy, whereas intermediate- and high-potency corticosteroids should be used for the treatment of clinical exacerbation over short periods of time. (A)

Summary statement 18. Potent fluorinated corticosteroids should be avoided on the face, the eyelids, the genitalia, and the intertriginous areas, as well as in young infants. (D)

Summary statement 19. Ultrahigh-potency corticosteroids should be used only for very short periods (several days) and only in areas that are lichenified. (D)

Summary statement 20. The degree of corticosteroid absorption through the skin, and hence the potential for systemic adverse effects, is directly dependent on the surface area of the skin involved, thickness of the skin, the use of occlusive dressing, and the potency of the corticosteroid preparation. (D)

Corticosteroids are effective medications for the treatment of atopic dermatitis.[4] However, patients should be carefully instructed in their use to avoid potential adverse effects. Certain areas, including the mucous membranes, the genitalia, the eyelids, the face, and intertriginous areas, have increased potential for transepidermal corticosteroid penetration, and for this reason, potent fluorinated corticosteroids should be avoided in these areas. A low-potency corticosteroid preparation is generally recommended for these areas. Patients should be instructed to apply topical corticosteroids to skin lesions and to use emollients over uninvolved skin. There are 7 classes of topical corticosteroids ranked according to their potency based on vasoconstrictor assays. Some of the commonly used ones are listed in Table 2. Group I includes the superpotent topical corticosteroids with the greatest potential for adverse effects, both localized and systemic. Group VII includes the least potent topical corticosteroids and, as a group, has the least potential for adverse effects. More potent topical corticosteroids may be used for several days in nonfacial, nonskinfold areas to treat acute rashes. Patients should then be instructed to reduce the potency of topical corticosteroids applied to their skin.

Because of their potential adverse effects, the ultrahigh-potency corticosteroids should be used for only very short periods of time and in areas that are lichenified and not on facial or skinfold areas. The high-potency corticosteroids should only be used for short periods of time (up to 3 weeks) for clinical exacerbations. Intermediate potency corticosteroids, such as 0.1% triamcinolone, can be used for longer periods of time to treat chronic atopic dermatitis involving the trunk and extremities. Corticosteroids in gel formulations usually contain a propylene glycol base and are irritating to the skin, in addition to promoting dryness, limiting their use to the scalp and beard areas. Compared with topical creams, ointments have enhanced topical potency.

Adverse effects from topical corticosteroids are directly related to the potency ranking of the compound and the duration of use. It is incumbent on the clinician to balance the need for therapeutic potency with the potential for adverse effects. Adverse effects from topical corticosteroids can be divided into local and systemic adverse effects. The latter, which occurs rarely, includes suppression of the hypothalamic-pituitary-adrenal axis. Local adverse effects include the development of striae and atrophy of the skin, perioral dermatitis, rosacea, and allergic contact dermatitis (due to the vehicle in most cases and after use of nonfluorinated corticosteroids). Systemic adverse effects are related to the potency of the topical corticosteroid, the site of application, the occlusiveness of the preparation, the percentage of the body covered, and the length of use. The potential for prolonged use of potent topical corticosteroids to cause adrenal suppression is greatest in small children and infants.[46,47]

Recent studies with 2 newer topical corticosteroids (fluticasone propionate and mometasone furoate) suggest that they have less systemic absorption and an efficacy profile that allows them to be used once as opposed to twice daily.[48,49] Furthermore, it has been reported that once control of atopic dermatitis is achieved with a daily regimen of topical corticosteroid, long-term control can be maintained with twice-weekly applications of topical fluticasone propionate to areas that have healed but are prone to developing eczema.[50]

Topical Calcineurin Inhibitors

Topical tacrolimus

Summary statement 21. Tacrolimus ointment has been shown to be effective and safe in both adults and children for the treatment of mild-to-moderately severe atopic dermatitis, with most patients experiencing a reduction of pruritus within 3 days of initiating therapy. (A)

Summary statement 22. Tacrolimus ointment applied on up to 100% of the body surface in adults and children has demonstrated sustained efficacy, with no significant systemic adverse effects. (A)

Table 2. Topical Glucocorticoid Potency Ranking

Group I	
	Betamethasone dipropionate 0.05% (cream and ointment)
	Clobestasol propionate 0.05% (cream and ointment)
	Diflorasone diacetate 0.05% (ointment)
	Halobetasol propionate 0.05% (cream and ointment)
Group II	
	Amcinonide 0.1% (ointment)
	Betamethasone dipropionate 0.05% (cream and ointment)
	Desoximetasone 0.25% (cream)
	Desoximetasone 0.05% (gel)
	Diflorasone diacetate 0.05% (ointment)
	Fluocinonide 0.05% (cream, gel, ointment, and solution)
	Halcinonide 0.1% (cream)
	Mometasone furoate 0.1% (ointment)
Group III	
	Amcinonide 0.1% (cream and lotion)
	Betamethasone dipropionate 0.05% (cream)
	Betamethasone valerate 0.1% (ointment)
	Desoximetasone 0.05% (cream)
	Diflorasone diacetate 0.05% (cream)
	Fluocinonide 0.05% (cream)
	Fluticasone propionate 0.005% (ointment)
	Halcinonide 0.1% (ointment and solution)
	Triamcinolone acetonide 0.1% (ointment)
Group IV	
	Hydrocortisone valerate 0.2% (ointment)
	Flurandrenolide 0.05% (ointment)
	Fluocinolone acetonide 0.025% (ointment)
	Mometasone furoate 0.1% (cream)
	Triamcinolone acetonide 0.1% (cream)
Group V	
	Betamethasone dipropionate 0.05% (lotion)
	Betamethasone valerate 0.1% (cream)
	Fluticasone acetonide 0.025% (cream)
	Fluticasone propionate 0.05% (cream)
	Flurandrenolide 0.05% (cream)
	Hydrocortisone valerate 0.2% (cream)
	Prednicarbate 0.1% (cream)
Group VI	
	Alclometasone dipropionate 0.05% (cream and ointment)
	Betamethasone valerate 0.05% (lotion)
	Desonide 0.05% (cream)
	Flucinolone acetonide 0.01% (cream and solution)
	Triamcinolone acetonide 0.1% (cream)
Group VII	
	Hydrocortisone hydrochloride 1% (cream and ointment)
	Hydrocortisone hydrochloride 2.5% (cream, lotion, and ointment)
	Hydrocortisone acetate 1% (cream and ointment)
	Hydrocortisone acetate 2.5% (cream, lotion, and ointment)
	Pramoxine hydrochloride 1.0% (cream, lotion, and ointment)
	Pramoxine hydrochloride 2.5% (cream, lotion, and ointment)

Summary statement 23. A local burning sensation is the most common adverse effect associated with tacrolimus. This may limit its usefulness in certain patients. (A)

Summary statement 24. Tacrolimus ointment can be used safely for facial and eyelid eczema. (D)

Tacrolimus is a drug that acts by binding with high affinity to a 12-kDa cytoplasmic macrophilin, and the complex inhibits the activity of calcineurin, a calcium-dependent phosphatase. This, in turn, inhibits the translocation of the transcription factor NF-AT into the cell nucleus, blocking the initiation of NF-AT–dependent gene transcription. Tacrolimus inhibits the activation of key cells involved in atopic dermatitis, including T cells, dendritic cells, mast cells, and keratinocytes.[18] Unlike cyclosporin, another well-known calcineurin inhibitor, tacrolimus exhibits activity when applied topically. Multicenter, blinded, vehicle-controlled studies with tacrolimus ointment, 0.03% and 0.1%, in both adults and children have reported topically applied tacrolimus to be effective and safe.[19,51–53] Local burning sensation is the only common adverse event. Most patients experience a reduction of pruritus within 3 days of initiating therapy. In adults, a dose-response effect was seen between 0.03% and 0.1% tacrolimus, particularly for patients with more severe skin disease. Atopic dermatitis patients treated with topical tacrolimus have been reported to have a significant improvement in quality of life.[20]

Tacrolimus ointment (Protopic) 0.03% has recently been approved for short-term and intermittent long-term use in moderate-to-severe atopic dermatitis in children 2 to 15 years of age. It has also been approved in the 0.03% as well as 0.1% concentration for adults. Long-term, open-label studies with tacrolimus ointment have been performed in adults and children with sustained efficacy and no significant adverse effects.[23,24] In addition, unlike topical glucocorticoids, tacrolimus ointment is not atrophogenic and has a greater therapeutic margin of safety than medium-strength glucocorticosteroids for facial and eyelid eczema.

Patients with steroid phobia should be started on a topical calcineurin inhibitor to encourage adherence with anti-inflammatory therapy. Furthermore, there is a group of patients with corticosteroid insensitivity who would benefit from early treatment with topical tacrolimus, since corticosteroid-resistant T cells have been found to respond well to tacrolimus.[54] Furthermore, patients with recalcitrant facial eruptions resistant to topical corticosteroids have reported benefit from use of topical tacrolimus.[55]

A multicenter, randomized, double-blind, parallel-group study comparing 0.03% and 0.1% tacrolimus ointment to a mid-potent topical corticosteroid, hydrocortisone-17-butyrate, ointment was performed in 570 adults with moderate-to-severe atopic dermatitis.[56] This 3-week study demonstrated that a 0.1% concentration of tacrolimus had a similar efficacy as 0.1% hydrocortisone-17-butyrate. Another randomized, double-blind, parallel-group study compared 0.03% and 0.1% tacrolimus ointment to a low-potency topical corticosteroid, 1% hydrocortisone acetate ointment, in 560 children 2 to 15

years old with moderate-to-severe atopic dermatitis.[57] Both 0.03% and 0.1% tacrolimus ointment were significantly more effective than 1% hydrocortisone acetate ointment in reducing skin inflammation due to atopic dermatitis. These 2 studies suggest that 0.1% tacrolimus ointment has the strength of a mid-potency topical corticosteroid and should be considered first-line therapy for facial eczema where treatment with corticosteroids is limited to low-potency topical corticosteroids because of safety concerns.

Concern has been raised regarding potential effects of this new class of topical calcineurin inhibitors on prevalence of local viral infections (eg, herpes simplex), so patients should be monitored for this possible complication.[58] In contrast, the number of staphylococcal *aureus* organisms on atopic dermatitis skin decreases with prolonged use of topical tacrolimus due to its effective control of skin inflammation.[59]

Topical pimecrolimus

Summary statement 25. Topical pimecrolimus cream is a calcineurin inhibitor that decreases the number of flares of atopic dermatitis, reduces the need for corticosteroids, and controls pruritus. (A)

Pimecrolimus is a novel ascomycin macrolactam derivative that binds with high affinity to its cytosolic receptor, macrophilin-12, and thereby inhibits calcineurin using a similar mechanism as tacrolimus. However, studies in experimental animals suggest that structural differences in lipophilicity endow pimecrolimus, compared with tacrolimus, with the ability to preferentially distribute to the skin as opposed to the systemic circulation.[60] In clinical studies, pimecrolimus blood levels have remained consistently low, with no clinically relevant drug-related systemic adverse events reported.[61] As a consequence of inhibiting calcineurin, pimecrolimus inhibits T-cell proliferation, prevents the gene transcription of T_H1 and T_H2 cytokines, and reduces mediator release from mast cells and basophils.[22] Topical application in humans has not been associated with the atrophy observed with topical corticosteroids.[25]

Short-term, multicenter, blinded, vehicle-controlled studies with pimecrolimus cream 1% patients with atopic dermatitis have shown pimecrolimus to be both effective and safe.[21] Significant relief of pruritus relative to the vehicle control was observed in the pimecrolimus-treated group at the first efficacy evaluation, 8 days after initial application of the study medication. Pimecrolimus cream 1% (Elidel) has recently been approved for short-term and intermittent long-term use in patients with mild-to-moderate atopic dermatitis who are 2 years and older. When used as long-term maintenance therapy, topical pimecrolimus has been found to reduce the number of exacerbations due to atopic dermatitis and to reduce the need for corticosteroid therapy.[26,62]

Tar Preparations

Summary statement 26. Although tar preparations are widely used in the treatment of atopic dermatitis, there are no randomized controlled studies that have demonstrated their efficacy. (A)

Summary statement 27. Newer coal tar products have been developed that are more cosmetically acceptable, with respect to odor and staining of clothes, than some older products. (B)

Summary statement 28. Tar preparations should not be used on acutely inflamed skin, since this may result in additional skin irritation. (D)

Crude coal tar extracts were used to reduce skin inflammation before the availability of topical corticosteroids. The anti-inflammatory properties of tars, however, are not well characterized. There are no well-controlled, randomized, vehicle-controlled studies with tar preparations.[4] Therefore, part of the improvement observed with tar preparations could be due to a placebo effect that can be significant in atopic dermatitis.

Newer coal tar products have been developed that are more cosmetically acceptable with respect to odor and staining of clothes than some older products.[63] To increase compliance, tar preparations may be recommended at bedtime. The preparation is then removed by washing in the morning, thus eliminating concern about odor during the day and limiting staining of daytime clothing. Tar preparations should not be used on acutely inflamed skin, since this may result in additional skin irritation. There is a theoretical risk of tar being a carcinogen based on observational studies of workers using tar components in their occupation. Adverse effects associated with tars include folliculitis and, occasionally, photosensitivity. Tar shampoos (T/Gel, Ionil T) are often beneficial when atopic dermatitis involves the scalp.

Antihistamines

Summary statement 29. Some patients may benefit from the use of antihistamines for the relief of pruritus associated with atopic dermatitis. (C)

Summary statement 30. Treatment of atopic dermatitis with topical antihistamines is generally not recommended because of potential cutaneous sensitization. (C)

Oral antihistamines are commonly prescribed for control of pruritus in atopic dermatitis. However, a recent evidence-based review of 16 controlled studies revealed little objective evidence demonstrating the relief of pruritus when sedating or nonsedating antihistamines were used in the treatment of atopic dermatitis.[64] Although the majority of these studies were flawed because of small sample size or poor study design, these observations are not surprising, since histamine is only one of many mediators released during the inflammatory response that can induce pruritus. In fact, reduction of skin inflammation with topical glucocorticoids and calcineurin inhibitors will often reduce pruritus.[19,21,48,51–53]

These observations, however, do not exclude the possibility that there are individual patients with atopic dermatitis who may benefit from use of antihistamines, particularly those patients with concomitant urticaria or allergic rhinitis.[65] Second-generation antihistamines may be effective in relieving symptoms of atopic dermatitis.[66–70] Since pruritus is usually worse at night, sedating antihistamines (eg, hydroxyzine or diphenhydramine) offer an advantage when used at bed-

time. If severe nocturnal pruritus persists, short-term use of a sedative to allow adequate rest may be appropriate.

Treatment of atopic dermatitis with topical antihistamines is generally not recommended because of potential cutaneous sensitization.[71] However, a multicenter, double-blind, vehicle-controlled study of topical 5% doxepin cream demonstrated a significant reduction of pruritus.[72] In this 1-week study, sensitization was not reported. However, sedation can occur with widespread application, and irritation has also been noted by patients.

IDENTIFICATION AND ELIMINATION OF TRIGGERING FACTORS

Summary statement 31. Avoidance of common irritants (eg, soaps, toiletries, wool, chemicals) that trigger the itch-scratch cycle is recommended. (B)

Summary statement 32. Control of temperature and humidity may be useful for preventing pruritus. (D)

Summary statement 33. Aeroallergens such as house dust mites, animal allergens, and pollens may cause exacerbation, and therefore exposure to them should be minimized. (A)

Summary statement 34. Possible triggers of atopic dermatitis can be confirmed by skin tests and in vitro tests for specific IgE antibodies and in some cases by patch tests, which may produce immediate or delayed reactions to protein allergens. (B)

Summary statement 35. Food allergens trigger atopic dermatitis more commonly in young infants and children than in adults. (D)

There is a lower threshold for irritation of the skin in patients with atopic dermatitis.[73] Therefore, it is important to identify and avoid irritants that trigger the itch-scratch cycle (Table 3). These include soaps, detergents, chemicals, abrasive clothing, and extremes of temperature and humidity. Alcohol and astringents found in toiletries are drying. Therefore, the use of soaps, solvents, and similar compounds should be avoided. When soaps are used, they should have minimal defatting activity and a neutral pH. Mild soaps include unscented Dove, Basis, Neutrogena, Aveeno, Lowila, Purpose, and Cetaphil. New clothing should be laundered before wearing to decrease levels of formaldehyde and other chemicals added for fabric sizing. Residual laundry detergent in clothing may be irritating. Using a liquid rather than powder detergent and adding a second rinse cycle will facilitate removal of the detergent. Occlusive, tight clothing should be avoided, and the patient should be advised to wear open-weave, loose-fitting cotton, or cotton-blend garments.

Recommendations regarding environmental living conditions should include temperature and humidity control to avoid increased pruritus related to heat, humidity, and perspiration. One goal of treatment is for children to be as normally active as possible. Certain sports such as swimming may be better tolerated than sports involving intense perspiration, physical contact, or heavy clothing and equipment, but patients must rinse off the chlorine after swimming immediately and lubricate their skin. Although ultraviolet light may be beneficial for some patients with atopic dermatitis, sunscreens should be used to avoid sunburn. However, since sunscreens can be irritants, care should be used to identify a nonirritating sunscreen. Prolonged sun exposure can lead to evaporative losses or sweating, both of which can be irritating, as well as produce photodamage.

Table 3. Triggers of Itching in Atopic Dermatitis*

All irritants	Lipid solvents (ie, soaps, detergents)
	Disinfectants (eg, chlorine in swimming pools)
	Occupational irritants
	Household fluids (eg, juices from fresh fruits, meats)
Contact and aeroallergens	Dust mites, contact > aeroallergens
	Furry animals (cat > dog)
	Pollens (seasonal)
	Molds
	Human dander (dandruff)
Microbial agents	Viral infections (especially upper respiratory tract infections)
	Staphylococcus aureus (either as a superantigen or pathogen)
	Pityrosporum ovale yeast
	Candida (rarely)
	Dermatophytes (rarely)
Others	Foods (as contact irritants > vasodilators > allergens)
	Psyche
	Climate
	Hormones (eg, menstrual cycle)

* Not all patients with atopic dermatitis will be triggered by every stimulus. There are subsets of patients with atopic dermatitis who will experience exacerbations by some triggers and not by others. Adapted from Beltrani VS. The clinical spectrum of atopic dermatitis. *J Allergy Clin Immunol.* 1999;104:S87–S98.

Foods and aeroallergens, such as dust mites, animal allergens, and pollens, may trigger atopic dermatitis. Potential allergens can be identified by taking a careful history and performing appropriate immediate hypersensitivity skin tests.[74,75] Intracutaneous skin tests to foods are not recommended, since they are relatively nonspecific, may trigger anaphylactic reactions, and do not provide reliable results in this patient population. Negative skin test or in vitro test results for aeroallergens have a high predictive value for ruling out suspected allergens. On the other hand, positive skin tests, particularly to foods, do not always correlate well with clinical symptoms and may need to be confirmed in the case of foods with a controlled food challenge and/or elimination diet.[5] Studies indicate that food-specific serum IgE concentrations may be useful for diagnosing symptomatic allergy to certain foods, such as egg, milk, peanut, and fish, and could eliminate the need to perform controlled food challenges in some patients.[76–78] However, the amount of food causing a reaction and the severity of the reaction are not predicted by prick skin testing or concentration of food-specific serum IgE.[79] If the patient has a history suggestive of

food allergy but there is no evidence of food-specific IgE antibodies, it may be necessary to perform an oral food challenge to rule out food sensitivity that is not IgE mediated.[80]

In children who have undergone double-blind, placebo-controlled food challenge, milk, egg, peanut, soy, wheat, and fish account for nearly 90% of the foods that exacerbate atopic dermatitis.[14] Avoidance of foods implicated by controlled food challenge has been shown to result in clinical improvement.[15,81] Extensive elimination diets, which in some cases can be nutritionally deficient, are rarely required, because, even with multiple positive skin test results, most patients will react to 3 or fewer foods on blinded challenge.

Pruritus and eczematoid skin lesions can develop after intranasal or bronchial inhalation challenge with aeroallergens in sensitized patients with atopic dermatitis who have specific IgE antibodies against the challenge allergen.[82,83] Epicutaneous application of aeroallergens (eg, house dust mites, weeds, animal danders, molds) by patch testing on uninvolved skin of patients with atopic dermatitis elicits eczematoid reactions in 30% to 50% of patients with atopic dermatitis, although the clinical significance of this finding is unclear.[84] In contrast, patch test results are usually negative in patients with respiratory allergy and healthy volunteers. Several studies have found that effective reduction in the level of house dust mites is associated with significant improvement in atopic dermatitis.[16,85–87] Avoidance of house dust mites may include (1) use of dust mite–proof encasings on pillows, mattresses, and box springs; (2) washing bedding in hot water weekly; (3) removal of bedroom carpeting; and (4) decreasing indoor humidity levels with air conditioning.[88]

Since there are many triggers that contribute to flares of atopic dermatitis, attention should be focused on controlling those trigger factors that are important in each patient, for example, infants and young children are more likely to have food allergy, whereas in older children and adults, environmental aeroallergens are more important in causing exacerbation of atopic dermatitis.

MICROBES

Summary statement 36. Patients with moderate-to-severe atopic dermatitis have been found to make IgE antibodies against staphylococcal toxins present on their skin. (B)

Summary statement 37. A course of an appropriate systemic antibiotic should be considered in patients who are heavily colonized or infected with staphylococcal *aureus*. Antibiotic treatment may be more difficult if *S aureus* is resistant. (D)

Summary statement 38. Atopic dermatitis can be complicated by recurrent viral skin infections, such as herpes simplex, warts, and molluscum contagiosum. (B)

Summary statement 39. Smallpox vaccination or even exposure of patients with atopic dermatitis to recently vaccinated individuals may cause a severe, widespread, potentially fatal dermatitis called *eczema vaccinatum*, which is similar in appearance to eczema herpeticum. (D)

Summary statement 40. Dermatophytic infections can complicate atopic dermatitis and may contribute to exacerbation of disease activity. (C)

Skin infections, particularly with staphylococcal *aureus*, can be a recurrent problem in atopic dermatitis, requiring specific treatment.[2] Patients with moderate-to-severe atopic dermatitis have been found to make IgE antibodies against staphylococcal toxins present on their skin.[6–8] Therefore, antistaphylococcal antibiotics may be very helpful in the treatment of patients who are heavily colonized or infected with *S aureus*. Erythromycin and the newer macrolide antibiotics (azithromycin and clarithromycin) are usually beneficial and safe for patients who are not colonized with a resistant *S aureus* strain. In patients with macrolide-resistant *S aureus*, a penicillinase-resistant penicillin (dicloxacillin, oxacillin, or cloxacillin) may be preferred. Cephalosporins also offer effective coverage for both staphylococci and streptococci.[9] In patients with extensive infection, a course of systemic antibiotics is preferred.

Increased binding of *S aureus* to skin is probably related to the underlying inflammation present in atopic dermatitis. This is supported by the observation that treatment with topical glucocorticoids or tacrolimus reduces *S aureus* counts on atopic skin.[59,89] Recent studies have demonstrated that T_H2 immune responses increase binding of *S aureus* to inflamed skin lesions and reduce local innate immune responses needed to kill *S aureus*.[90–92]

Atopic dermatitis can be complicated by recurrent viral skin infections such as herpes simplex, warts, and molluscum contagiosum, which may reflect local defects in T-cell function.[93] Herpes simplex, resulting in Kaposi's varicelliform eruption or eczema herpeticum, can be a serious infection. The presence of punched-out erosions, vesicles, and/or infected skin lesions that fail to respond to oral antibiotics should initiate a search for herpes simplex. Herpes simplex infection can be diagnosed by a Giemsa-stained Tzanck smear of cells scraped from the vesicle base, commercial immunofluorescence assays, or viral culture. Antiviral treatment for cutaneous herpes simplex infections is of critical importance in the patient with widespread atopic dermatitis, since life-threatening dissemination has been reported.[94,95] In patients with atopic dermatitis, smallpox vaccination or even exposure to recently vaccinated individuals may cause a severe, widespread, life-threatening dermatitis called *eczema vaccinatum*, which is similar in appearance to eczema herpeticum.[96] In the event of a smallpox bioterrorist attack, patients with atopic dermatitis would be at increased risk for developing this complication.

Dermatophyte infections can complicate atopic dermatitis and may contribute to exacerbation of the disease. There has been particular interest in the role of *Malassezia furfur* (*Pityrosporum ovale*) in patients with atopic dermatitis. *M furfur* is a lipophilic yeast commonly present in the seborrheic areas of the skin and in the scalp. IgE antibodies against *M furfur* are commonly found in patients with atopic dermatitis, most frequently in patients with involvement of the head and

neck.[97] The potential importance of *M furfur,* as well as other dermatophyte infections, is further supported by a reduction in the severity of atopic dermatitis following treatment with antifungal agents.[98]

EMOTIONAL STRESS

Summary statement 41. Emotional factors do not cause atopic dermatitis but often cause exacerbation (D) and have been found to induce immune activation as well as increase pruritus and scratching. (LB)

Patients with atopic dermatitis can have significant problems with anxiety, anger, and hostility.[99] Although these emotional factors do not cause atopic dermatitis, they often cause exacerbation and have been found to induce immune activation in patients with this condition.[100,101] Atopic patients often respond to stress, frustration, embarrassment, or other upsetting events with increased pruritus and scratching.[102] In some patients, scratching is associated with significant secondary gain or simply occurs out of habit. Psychological evaluation and/or counseling should be considered in patients who have difficulty with emotional triggers or who have psychological problems that make it more difficult to manage their disease. Such evaluation and counseling may be especially useful in adolescents and young adults who consider their skin disease disfiguring. Relaxation, behavioral modification, or biofeedback may be helpful, particularly in those patients with habitual scratching.[103,104]

PATIENT EDUCATION

Summary statement 42. To achieve effective control of atopic dermatitis, it is important to educate patients and family members about the chronic nature of atopic dermatitis, exacerbating factors, and appropriate treatment options, including patient support organizations to enhance adherence. (D)

To achieve effective control of atopic dermatitis, it is important to educate patients and family members about the chronic nature of their disease, exacerbating factors, and appropriate treatment options. This is important to ensure cooperation and compliance with the treatment plan. Written information that includes detailed skin care recommendations and methods for environmental control, as well as general information about atopic dermatitis, can be helpful. Patients should be educated on how to monitor atopic dermatitis, how to respond to changes in their status, and when to seek additional medical help.

The treatment plan should be reviewed during each follow-up visit, and the patient or parent should demonstrate an appropriate level of understanding to ensure a good outcome. Adequate time and teaching materials are necessary to provide effective education. Patient support organizations that provide updates on progress in atopic dermatitis research are important resources for these patients. Educational pamphlets and videos may be obtained from the Eczema Association for Science and Education (1221 SW Yamhill, Suite 303, Portland, OR 97205; 503-228-4430), a national, nonprofit, patient-oriented organization, or from the American Academy of Dermatology's Web site Eczemanet.

TREATMENT OF THE DIFFICULT-TO-MANAGE PATIENT

Wet Dressings and Occlusion

Summary statement 43. Wet dressings may serve as an effective barrier against persistent scratching, allowing more rapid healing of excoriated lesions. (B)

Summary statement 44. Application of wet-wrap dressings in combination with topical corticosteroids can be efficacious in the treatment of refractory atopic dermatitis. (A)

Wet dressings can be used on severely affected or chronic lesions refractory to skin care.[27,28] Dressings may serve as an effective barrier against persistent scratching and encourages healing of excoriated lesions. Application of wet-wrap dressings in combination with topical corticosteroids has been found to be efficacious in the treatment of refractory atopic dermatitis because of better absorption.[27,105] However, patients should be monitored carefully for secondary microbial infection and adrenal suppression when wet-wrap dressings are used for prolonged periods in combination with potency corticosteroids.

Allergen Immunotherapy

Summary statement 45. Although the effectiveness of allergen immunotherapy in the treatment of atopic dermatitis has not been conclusively demonstrated, there are selected patients with atopic dermatitis who may benefit from such treatment. (A)

Unlike allergic rhinitis and asthma, there is no conclusive evidence that immunotherapy with aeroallergens is effective in the treatment of atopic dermatitis, although there are selected individuals who may benefit from such treatment.[106–109] Expert opinion supports the use of allergen immunotherapy for selected individuals.

Systemic Glucocorticosteroids

Summary statement 46. The use of systemic corticosteroids may be required in the treatment of severe, recalcitrant chronic atopic dermatitis. (F)

Summary statement 47. The dramatic clinical improvement that may occur after administration of systemic corticosteroids may be associated with an equally dramatic rebound flaring of atopic dermatitis following discontinuation of systemic corticosteroids. (F)

The use of systemic corticosteroids, such as oral prednisone, may be required in the treatment of severe chronic atopic dermatitis. However, the dramatic clinical improvement that may occur with systemic corticosteroids may be associated with an equally dramatic rebound flaring of atopic dermatitis following the discontinuation of systemic corticosteroid therapy. If a short course of oral corticosteroid therapy is given for a patient with severe atopic dermatitis, it is important to taper the dosage as it is discontinued. Intensified skin care, particularly with topical corticosteroids and frequent bathing followed by application of emollients, should also be instituted during the corticosteroid taper to suppress rebound flaring of atopic dermatitis. Patients who require more than one course of

oral corticosteroid therapy should be evaluated by an allergist or dermatologist to determine if factors contributing to poorly controlled atopic dermatitis can be identified and eliminated or whether an incorrect diagnosis has been made.

Phototherapy

Summary statement 48. Natural sunlight can be beneficial for atopic dermatitis, but sunburn and overheating should be avoided. (D)

Summary statement 49. Ultraviolet therapy can be a useful adjunct in the treatment of recalcitrant atopic dermatitis. (A)

Summary statement 50. Phototherapy with PUVA should be restricted to patients with recalcitrant atopic dermatitis. (D)

Natural sunlight frequently is beneficial to patients with atopic dermatitis, although sunburn should be avoided. If the sunlight occurs in the setting of high heat or humidity, which triggers sweating and pruritus, exacerbation of atopic dermatitis may occur. Ultraviolet light therapy can be a useful adjunct in the treatment of chronic, recalcitrant atopic dermatitis but should be administered by a health care professional experienced in such treatment. This form of therapy is best performed under the supervision of a dermatologist. Broad-band ultraviolet B, broad-band ultraviolet A, narrow-band ultraviolet B (311 nm), ultraviolet A-1 (340 to 400 nm), and combined ultraviolet AB phototherapy can be useful adjuncts in the treatment of atopic dermatitis.[29,110,111] Photochemotherapy with PUVA should be restricted to patients with severe, widespread atopic dermatitis, although studies comparing it with other modes of phototherapy are limited. Short-term adverse effects from phototherapy may include erythema, skin pain, pruritus, and pigmentation. Potential long-term adverse effects include premature skin aging and cutaneous malignancies.

Systemic Immunomodulating Agents

Summary statement 51. Immunosuppressive agents such as cyclosporin, interferon gamma, mycophenolate mofetil, and azathioprine have been shown to provide benefit for certain cases of severe refractory atopic dermatitis, but potential benefits should be weighed against their potentially serious adverse effects. (B)

Cyclosporin

Systemic cyclosporin A is a potent immunosuppressive drug that acts primarily on T cells by suppressing cytokine gene transcription. The drug binds to an intracellular protein, cyclophilin, and this complex in turn inhibits calcineurin, a molecule required for initiation of cytokine gene transcription. Several randomized controlled studies have demonstrated that both children and adults with severe atopic dermatitis refractory to conventional treatment can benefit from short-term treatment with oral cyclosporin (5 mg/kg per day) in terms of reduced skin disease and improved quality of life.[112–114] However, adverse effects (nausea, abdominal discomfort, hypertrichosis, paresthesias, hypertension, hyperbilirubinemia, and renal impairment) dictate caution in the use of this drug. Furthermore, discontinuation of treatment frequently results in rapid relapse of skin disease.[115]

Interferon gamma

Interferon gamma is available as a recombinant molecule for the treatment of chronic granulomatous disease. It is also known to down-regulate T_H2 cell function. Studies of patients with atopic dermatitis have demonstrated that treatment with recombinant interferon gamma results in clinical improvement and decreases total circulating eosinophil counts.[30,116] In one study, a small subset of patients showed persistent improvement 3 months after treatment was discontinued.[117] Reduction in clinical severity of atopic dermatitis correlated with the ability of interferon gamma to decrease blood eosinophilia. In another study in which patients with atopic dermatitis were treated for up to 24 months, total body surface involvement decreased from 62% at baseline to 18.5% after 24 months of treatment.[118] Long-term therapy was not associated with any significant laboratory abnormalities or clinical adverse events. However, influenza-like symptoms are commonly observed adverse effects early in the treatment course and limit the use of this therapy.

Mycophenolate mofetil

Mycophenolate mofetil is a purine biosynthesis inhibitor with immunosuppressive activity that has been used for treatment of refractory inflammatory skin disorders.[31,119] Short-term oral mycophenolate mofetil, 2 g/d, as monotherapy has been reported in open-label studies to clear skin lesions in some adults with atopic dermatitis resistant to other treatment, including topical and oral steroids and PUVA. The drug has generally been well tolerated, with the exception of occasional herpes retinitis and dose-related bone marrow suppression.

Azathioprine

Azathioprine is a purine analog with anti-inflammatory and antiproliferative effects. It has been utilized for severe atopic dermatitis, although no controlled studies have been reported.[32,120] Myelosuppression is a significant adverse effect, and thiopurinemethyl transferase levels may predict individuals at risk for severe adverse effects from this drug.

Hospitalization

Summary statement 52. Hospitalization can result in an improvement in atopic dermatitis by removing the patient from environmental allergens and irritants and by providing patient education and improving compliance. (F)

Patients with moderately severe, nonresponsive atopic dermatitis who appear erythrodermic or have widespread, severe skin disease resistant to outpatient therapy may require hospitalization. In many cases, removing the patient from environmental allergens or irritants, intense patient education, and assurance of compliance with therapy result in sustained improvement. Clearing of the patient's skin during hospitalization also allows the patient to undergo allergen skin testing and appropriately controlled provocative challenges to correctly identify potential allergens.

Investigative Approaches

Summary statement 53. There are certain investigative treatments that have been proposed for the treatment of atopic dermatitis. These remain unproven at this time. (D)

Chinese herbal therapy. Placebo-controlled clinical studies have suggested that patients with severe atopic dermatitis may benefit from treatment with Chinese herbs.[121,122] The beneficial response from Chinese herbal therapy, however, is often temporary, and effectiveness may wear off despite continued treatment. The possibility of significant adverse effects associated with long-term use remains a concern.

Leukotriene antagonists. Increased levels of leukotrienes have been measured in patients with atopic dermatitis.[123,124] Small randomized studies of leukotriene antagonists have suggested beneficial effects in reducing the severity of atopic dermatitis.[125,126]

Mycobacterium vaccae. Children with moderate-to-severe atopic dermatitis were enrolled in a randomized, double-blind, placebo-controlled study, where they were given either one intradermal injection of killed *Mycobacterium vaccae* or placebo.[127] Children treated with *M vaccae* showed a significantly greater improvement in severity of skin disease than patients treated with placebo. These observations suggest that down-regulation of the T_H2 response in atopic dermatitis may have potentially beneficial effects.

Consultation

Summary statement 54. Patients refractory to first-line therapy should be evaluated by an atopic dermatitis specialist. (F)

Cooperation between the patient and/or the patient's guardian(s), the primary care physician, and the allergist or dermatologist is important in the implementation of strategies necessary for the care of patients with chronic atopic dermatitis. The primary care physician plays an important role in the routine care of patients with uncomplicated atopic dermatitis, ensuring continuity of care. Consultation with an allergist or dermatologist is recommended (1) for patients with severe atopic dermatitis who have significant dysfunction as a result of their skin disease; (2) for identification of potential allergen triggers; (3) for patient education; (4) when the diagnosis of atopic dermatitis is in doubt; and (5) for implementation of alternative therapies.

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Exhibit B

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International Consensus Conference on Atopic Dermatitis II (ICCAD II*): clinical update and current treatment strategies

C.ELLIS* AND T.LUGER† ON BEHALF OF THE ICCAD II FACULTY: D.ABECK, R.ALLEN, R.A.C.GRAHAM-BROWN, Y.DE PROST, L.F.EICHENFIELD, C.FERRANDIZ, A.GIANNETTI, J.HANIFIN, J.Y.M.KOO, D.LEUNG, C.LYNDE, J.RING, R.RUIZ-MALDONADO AND J-H.SAURAT

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Atopic dermatitis

Atopic dermatitis (AD) is a common chronic relapsing inflammatory skin disease, characterized by intense itching, dry skin, inflammation and exudation. It causes physical and emotional distress for patients and their families. The first symptoms commonly develop in infancy, with around 50% of cases diagnosed by 1 year of age,[1] and AD is typically a long-term condition with at least one-third of patients having persistent disease throughout adulthood. However the vast majority of cases of atopic dermatitis are mild in severity and usually can be managed easily.[2] The disease is often familial and frequently associated with asthma, food allergy, allergic rhinitis and recurrent secondary skin infections. Atopic dermatitis has significant impact on quality of life in both children[3] and adults.[4] The impact is greater than with psoriasis and is equivalent to other serious medical conditions such as early onset of diabetes mellitus.[5] The prevalence of atopic dermatitis has increased steadily in recent decades.[4] In developed countries approximately 10–15% of children under 5 years of age are affected at some stage.[4] The likelihood is that 60% of children with atopic dermatitis may recover free of the disease, the remainder having recurrences for long periods of time.[6] It has also been suggested that the best prognosis for the disease is in those children who developed AD in the first year of life.[7] However, overall the earlier the onset and the more severe the disease, there is a greater chance of persistence, especially with concurrent atopic disorders. Recent evidence has indicated a common pathophysiological link between severe atopic dermatitis, asthma and allergic rhinitis[8,9] (for example both asthma and AD are associated with increased IgE and eosinophilia). It has been suggested that atopic dermatitis may increase the subsequent risk or severity of asthma.[10]

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*The first ICCAD meeting was held in Rome in 1999, the proceedings of which were published in the *Journal of the American Academy of Dermatology* (2001;45: S1–67).

Current management of atopic dermatitis

At present there is no 100% life-long cure for atopic dermatitis. Management comprises a disease adapted treatment combining adjuvant basic therapy (skin protection) and, if needed, anti-inflammatory measurements and the identification and avoidance of trigger factors.[11,12] Treatment currently focuses on symptomatic relief (skin hydration and reduction of pruritus).[13–15]

Therapeutic options

Adjuvant basic therapy As the barrier function of the skin in patients with atopic dermatitis is impaired, an adjuvant basic therapy is essential in the management of this disease consisting of the regular application of adequate moisturizers. Different classes of moisturisers are based on their mechanism of action, including occlusives, humectants, emollients and protein rejuvenators. Patients may be prescribed different moisturizers depending on their particular preference, their age and their type of eczema. Emollients keep the skin hydrated and can reduce itching. They should be applied regularly at least twice during the day, even when there are no symptoms of disease and should also be applied after swimming or bathing.

Topical steroids as the current standard for anti-inflammatory therapy Intermittent use of topical corticosteroids to treat the signs and symptoms of atopic dermatitis, in conjunction with emollients, has been the standard

disease management. Topical corticosteroids are often prescribed intermittently for short-term reactive treatment of acute flares and supplemented by emollients. Reactive treatment with corticosteroids offers rapid and effective symptomatic relief for acute flares. However, there are considerable safety concerns associated with their use, particularly when they are applied continuously. Potential adverse events are primarily cutaneous (principally skin atrophy, but also telangiectasia, hypopigmentation, steroid acne, increased hair growth and rosacea-like eruptions), but there may be systemic effects (suppression of the hypothalamic-pituitary-adrenal (HPA) axis, growth retardation, increased risk of glaucoma cataract and Cushing's syndrome).[16–20] These safety concerns have led to restrictions on the intensity and duration of topical corticosteroid use, especially in children and on delicate skin areas such as the face, neck and skin folds.

Topical corticosteroids may be a challenge to use. Patients or parents may be concerned about side-effects. The numerous products, and where to apply each specifically, may confuse patients. Generic products appear to patients to have different names, even though the active molecule is the same; patients may be guessing which product to use. The generic product may have different potency than the brand product when put into clinical use.

Other treatment options

A range of other treatment options is available for atopic dermatitis, including systemic corticosteroids or other pharmacological interventions such as cyclosporine[21] or azathioprine. These are generally reserved for severe cases that prove refractory to conventional treatment with topical agents. Long-term treatment with mycophenolate mofetil has also been successfully used in severe atopic dermatitis.[22]

Sedating antihistamines may be used for intense pruritus causing sleep disturbance. Physical therapies such as phototherapy and wet wraps are also employed in some instances. Intermittent use of topical and oral antibiotics can be helpful in cases where *S. aureus* overgrowth is prominent.[23] Appropriate counseling may be offered to patients in whom atopic dermatitis is exerting a pronounced psychological impact.

There is considerable dissatisfaction with existing standard pharmacological and physician interventions[14,24,25] and some patients explore 'alternative' therapies, such as Chinese herbal remedies, homeopathy or acupuncture, although there is limited evidence to evaluate their effectiveness.[26]

Avoidance of trigger factors

Atopic dermatitis can be provoked by a number of trigger factors. Among these are irritants (inappropriate clothing, water hardness, etc.), microbes (especially *Staphylococcus aureus*), psychological (especially stress situations) and allergic factors. Atopic dermatitis patients often have raised serum IgE levels and a high degree of sensitization to environmental allergens including foods. Indoor or outdoor pollutants such as tobacco smoke influence IgE production.[9] Up to one-third of children with atopic dermatitis may have a coexisting food allergy.[27] Trigger factors should if possible be identified and avoided. However, further research is needed to more clearly identify triggers as well as avoidance tactics. Allergological investigations rarely have therapeutic consequences in mild to moderate cases of atopic dermatitis.

Limitations of current treatment strategies

In many patients, the atopic dermatitis is poorly controlled. Topical corticosteroids are often reserved for flares that have become fully manifest. Lack of confidence in corticosteroid safety also adversely affects compliance and under-treatment of children with atopic dermatitis is common owing to physicians' and parents' concerns about the side-effects of corticosteroids.[24] Systemic treatment is associated with potentially severe adverse effects and is not recommended except as a last resort.[14] Phototherapy is inconvenient and may carry a risk of future skin cancers and/or photoageing. The immunosuppressants, including cyclosporine and azathioprine, require appropriate monitoring because of their potential effects on organ toxicity, increased risk of infection and possibly lymphoma and may interfere with immunization during childhood. There is also a need for controlled studies with allergen-specific immunotherapy, where some benefit has been shown in atopic dermatitis.

Therapeutic objectives for atopic dermatitis

In the absence of a cure, the therapeutic objectives for atopic dermatitis can be defined as follows:

- reduce signs and symptoms;
- prevent or reduce recurrences;

- provide long-term management by preventing exacerbation;
- modify the course of the disease.

Conventional therapies focus on the reactive treatment of relapses. There is a need for new safe and effective therapies for early control and long-term maintenance.

New developments: the role of new and emerging treatments

New and emerging therapies such as the topical calcineurin inhibitors, tacrolimus and pimecrolimus, not only complement existing treatment options but also overcome some of the drawbacks of topical steroid therapy and fulfil the long-term needs of patients in preventing disease progression. Their primary mechanism of action, which is distinct from topical corticosteroids, is to inhibit inflammatory cytokine transcription in activated T cells and other inflammatory cells through inhibition of calcineurin.[28,29]

Unlike many corticosteroids, these agents may be used on all body locations for extended periods. Their potencies are standard and there are no generic substitutes. Skin atrophy, glaucoma, and other local risks of corticosteroids do not occur, nor do the systemic side-effects such as HPA-axis suppression and growth retardation.

Pimecrolimus

Pimecrolimus exhibits high anti-inflammatory activity in models of skin inflammation,[28–30] but has only low activity in models of systemic immunosuppression.[30,31] Pimecrolimus 1% cream, specifically developed for the treatment of inflammatory skin diseases, has been shown to offer a safe and effective treatment option in a broad spectrum of atopic dermatitis patients, including infants,[32] children[33] and adults[34–36] with mild-to-severe disease even in highly sensitive skin areas.[37,38] More importantly (when used in the early stages) it has also been proven to have significant therapeutic advantages over conventional therapy (emollients plus topical corticosteroids) in the long-term management of atopic dermatitis.[39]

The results from short-term[37,40,41] and long-term[42] controlled clinical trials demonstrate its rapid and sustained effect in controlling pruritus, which is the primary complaint of patients with atopic dermatitis and is often the main indication for use of corticosteroids. In the controlled long-term study in adults[43] a significant effect ($P < 0{\cdot}001$), of pimecrolimus treatment on pruritus relief could be seen as early as Day 3 when compared to a conventional treatment. Relief from pruritus with pimecrolimus cream is also demonstrated across a diverse patient population in terms of age (> 3 months)[40] and severity of disease.[43] Pimecrolimus also provides significantly better long-term control of atopic dermatitis than a conventional treatment by preventing progression of disease to flare.[43–45] In large, controlled studies, significantly more patients in the pimecrolimus groups remained flare-free at 6 and 12 months when compared to a conventional-treatment group. For example, in the pimecrolimus group, 61% of patients remained flare-free during the first 6 months of the study in contrast to only 34% of patients treated conventionally ($P < 0{\cdot}001$).[44] The beneficial effect of pimecrolimus cream is also sustained over time with 51% of pimecrolimus patients vs. 28% in the conventional treatment group remaining flare-free at 12 months ($P < 0{\cdot}001$).[44] The ability of pimecrolimus to prevent flare progression also results in a significant steroid-sparing effect.[43–45] In a large study in infants, 64% of pimecrolimus patients required no steroids throughout the 12 months of the study, compared to 35% of those subjects treated conventionally.[45]

The potential for pimecrolimus to prevent flare progression and improve disease control is confirmed by a clear trend towards a significant reduction in use of pimecrolimus over time, which was seen in both large, long-term paediatric studies.[44,45]

Tacrolimus

Topical tacrolimus, an ointment formulation[46] of the oral systemic immunosuppressive agent used to prevent allotransplant rejection, has shown efficacy and safety for the treatment of atopic dermatitis in both short-term, double-blind[47] and long-term, open-label[48] clinical studies.

Tacrolimus ointment has a rapid and sustained effect on signs and symptoms of atopic dermatitis in adults[49] and children[50] with moderate-to-severe atopic dermatitis. In two long-term, open-label studies[48,49] an improvement was seen in all symptomatic parameters after 1 week of therapy. This improvement was maintained over 12 months.

The ability of tacrolimus ointment to clear atopic dermatitis was investigated in two short-term, vehicle controlled studies. In one study, 41% of patients treated with 0·1% tacrolimus ointment had ≥ 90% clearance

of disease at the end of the 12 weeks compared to only 7% in the vehicle treatment group ($P < 0{\cdot}001$).[49]

Two recent short-term (3-week) studies, in children (2–15 years)[51] and adults[52] with moderate-to-severe AD compared tacrolimus ointment (0·1% and 0·03%) and conventional treatment with a topical corticosteroid. In adults, tacrolimus was compared with a topical corticosteroid of mid-potency, hydrocortisone-17-butyrate ointment 0·1%. In children, the comparator was the low-potency hydrocortisone acetate ointment 0·1%. The results confirmed the efficacy of tacrolimus ointment compared to these topical corticosteroids and showed a quick onset of efficacy. In the study with children, there was a trend for the 0·1% tacrolimus to be more effective than 0·03% tacrolimus and for both formulations to be more effective than hydrocortisone acetate.[51] There were no serious safety concerns in either trial, with the only significant adverse event being transient skin burning and irritation.

This, together with the clinical data from pimecrolimus, reinforces the role of topical calcineurin inhibitors as maintenance therapy for atopic dermatitis with corticosteroids being reserved for acute control of disease progression.

Safety of the new treatments

Pre-clinical and clinical findings

When discussing safety of the new topical calcineurin inhibitors, two aspects have to be considered:

- potential systemic exposure due to percutaneous absorption;
- and local adverse events.

Percutaneous absorption of tacrolimus in healthy volunteers has been shown to be generally low.[53] Although in patients with atopic dermatitis, tacrolimus blood levels have been shown to be dose-dependent,[54] broadly related to the severity of the disease and degree of lichenification the majority had low tacrolimus blood levels and these have shown to decrease over time.[54–56]

Systemic blood levels of pimecrolimus have been shown to be consistently low and independent of duration of therapy (3 weeks to 1 year) and age of patients. There were no significant increases in systemic blood levels with increasing extent of body surface involvement (up to 92% TBSA).[57] As with tacrolimus, no long-term accumulation has been reported with pimecrolimus.[36,57] In the clinical trials both pimecrolimus and tacrolimus have shown no significant systemic toxicity.[43–45,55,56]

Skin atrophy, a local adverse event, long associated with topical corticosteroids, was not seen in any of the clinical trials with pimecrolimus or tacrolimus. In contrast to topical corticosteroids, tacrolimus and pimecrolimus have been shown to be also safe for application to particularly sensitive areas such as the face and neck.[56,57]

The most common important local-site reaction with topical tacrolimus and pimecrolimus is local discomfort associated with the application of the drug. In the tacrolimus clinical trials (with 0·03% ointment) up to 36% of paediatric patients[58–60] and up to 47% of adult patients[47,58] exposed to the study medication experienced a local burning sensation at time of application. Pimecrolimus cream 1% demonstrated a comparable level of application-site burning to conventional treatment with only 7·4% vs. 7·4%, respectively, reporting burning sensation in the long-term paediatric studies.[61] Also, in adult patients 10·4% of the pimecrolimus group experienced application-site burning compared to 3·1% in the conventional treatment group.[43] Application site burning is, however, transient and of short duration.

Given the mechanism of action, the possibility of local immunosuppression with topical tacrolimus and pimecrolimus is a potential concern. However, the risk of local bacterial infections is less in patients treated with topical calcineurin inhibitors than in patients on topical corticosteroids.[62] It is important to note that corticosteroids act on a broad spectrum of immune competent cells, including Langerhans' cells that have a key function in the local immunosurveillance. In clinical studies with pimecrolimus secondary skin infections occurred at similar rates as those patients treated with placebo.[45] With both compounds there is a decreased rate of skin infection over increasing length of use.[45,63]

With tacrolimus ointment in a 52-week photocarcinogenicity study, the median time to onset of skin tumour formation was decreased in hairless mice as compared to vehicle-treated animals, following chronic topical dosing with concurrent exposure to UV radiation (40 weeks of treatment followed by 12 weeks of observation) with tacrolimus ointment.[64] The risk of photocarcinogenicity is still undetermined in humans. In a similar study with pimecrolimus, there was a decrease in median time to onset, with vehicle cream alone, but this was unchanged with the addition of pimecrolimus.[65] It is nevertheless prudent for patients to minimize natural or artificial sunlight exposure whilst using the topical treatments.

In summary, the new topical calcineurin inhibitors seem to be extremely safe without many of the side-effects associated with conventional treatment for atopic dermatitis.

Treatment strategies/treatment guidelines

Algorithm

The treatment of atopic dermatitis must be based on an initial assessment of disease history, extent, and severity, including assessment of psychological distress and impact on the family (Fig. 1). The physician–patient communication is of utmost importance to secure compliance with treatment.

The initial treatment of atopic dermatitis consists of the liberal use of emollients for skin hydration. This should be coupled with education for both patients and caregivers on the avoidance of trigger factors.

Also, when the patient is already in flare, short-term use of topical corticosteroids is indicated to treat the acute disease. Topical calcineurin inhibitors are alternatives for acute control of pruritus and inflammation. Once the condition settles they can then revert to continuous use of emollients.

For maintenance therapy (in the case of persistent disease or frequent recurrences), topical calcineurin inhibitors can be used as well (Fig. 1). Pimecrolimus was used in clinical studies at the first sign or symptom of atopic dermatitis. It has been proven to prevent disease progression[43–45] and reduce the incidence of flares, with corticosteroids being reserved for acute exacerbations. Once the patient is back in remission emollients should be continued. It should be noted that the currently available data demonstrate that pimecrolimus can prevent flare progression. Tacrolimus studies have shown efficacy in long-term atopic eczema therapy,[47,48] but its effect on incidence of flares has not been studied.

Use as described above is possible because of the safety profile established in long-term trials of topical calcineurin inhibitors together with the proven ability of pimecrolimus to prevent progression of disease and improve disease control compared to conventional treatment (topical corticosteroids and emollients).[43–45] It also optimizes the role of corticosteroids, which are highly efficacious in treating acute exacerbations, whilst minimizing the risks by decreasing the time for which they are used.

Additional benefits of the treatment recommendations:

- it is easily communicated to patients;
- different areas of the skin can be treated in different ways depending on the activity of the condition;
- development of a clearly understood and effective treatment strategy should minimize the likelihood of patients seeking alternative and unproven therapies;
- this approach should help to standardize or harmonize the evaluation and treatment of the patient across clinical specialties;
- the treatment algorithm complements but extends current practice by allowing more individualization of treatment according to patient need.

Adjunctive therapy

In conjunction with drug treatment, adjunctive measures may also be necessary to maximize the outcome for individual patients. This may range from education on the avoidance of trigger factors to providing psychological support.

Infections can alter the course of the disease. In the event of patients developing either a bacterial, fungal or viral skin infection, the infection needs to be fully evaluated and appropriate antibiotic, antifungal or antiviral therapy should be initiated as soon as possible. Before commencing treatment with anti-inflammatory agents, clinical infections at treatment sites should be cleared.

Special emphasis should be put on treating reservoirs of the disease, i.e. nose and the groin, to prevent recurrence.

If the symptoms of atopic dermatitis are refractory and the condition cannot be brought under control by treatment with topical calcineurin inhibitors and intermittent use of corticosteroids, a range of options could be considered depending on the status of the individual patient. These include phototherapy, drug therapy with more potent topical or oral steroids, immunosuppressants such as cyclosporin, methotrexate or azathioprine alone or in combination with psychotherapeutic and psychopharmacological options.

In conclusion, there is a need for an effective and safe therapy for early control and long-term maintenance of atopic dermatitis, irrespective of the age of the patient. Topical corticosteroids have been the standard of therapy for many years and while their efficacy is not in question there are continuing concerns about their safety. The new class of topical calcineurin inhibitors may fulfil this unmet need by providing a safe and effective option for the long-term control of atopic dermatitis.

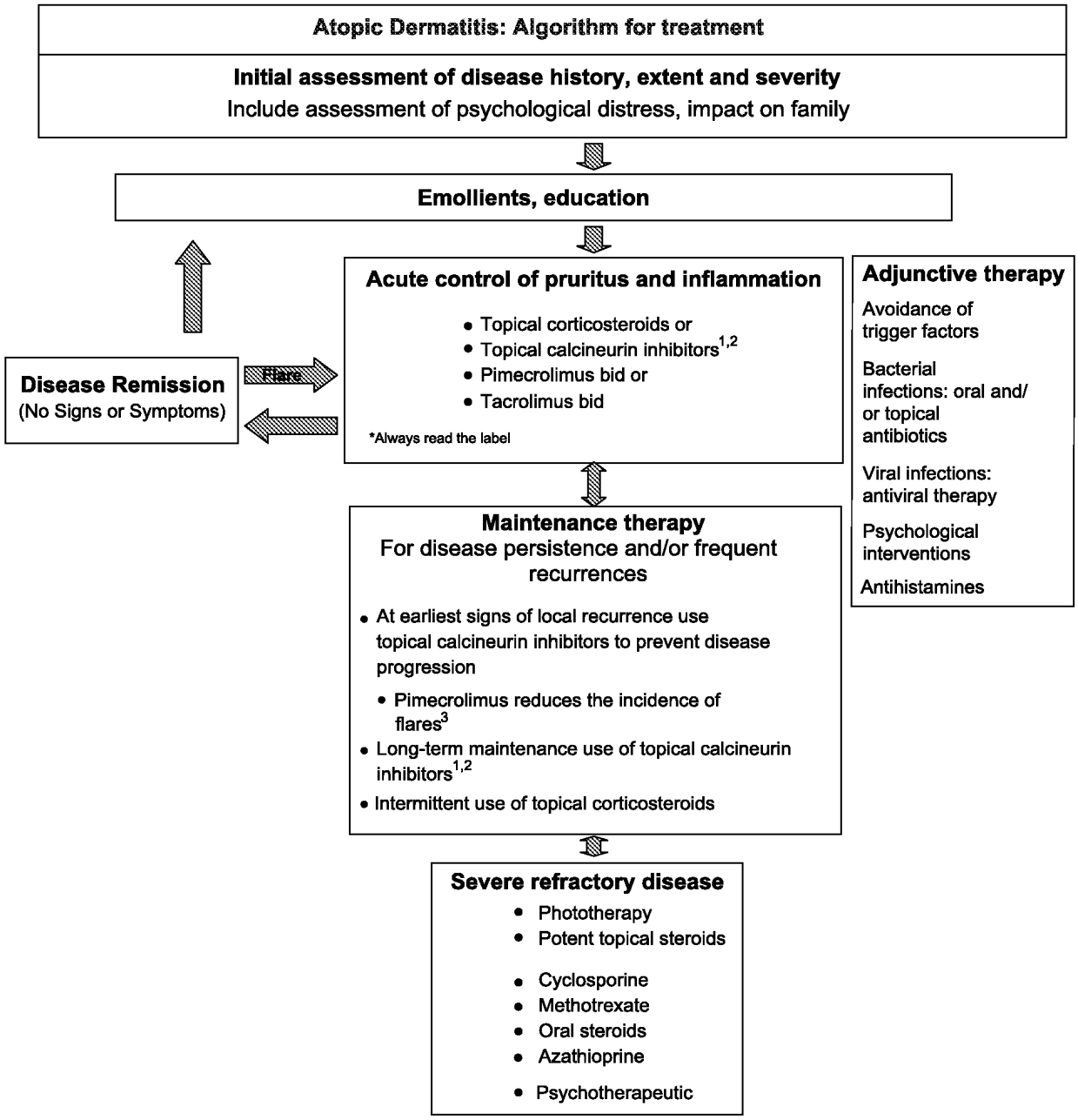

Figure 1. Algorithm for treatment of atopic dermatitis.

These new treatments for atopic dermatitis are welcomed by patients, parents of patients, and physicians including dermatologists and paediatricians, as another treatment option for this demoralizing disease, and the first major advance in its management in half a century.

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Exhibit C

CLINICAL REVIEW

Diagnosis and Treatment of Rosacea

Aaron F. Cohen, MD, and Jeffrey D. Tiemstra, MD

Background: **Rosacea is a common skin disorder affecting middle-aged and older adults. Many patients mistakenly assume that early rosacea is normally aging skin and are not aware that effective treatments exist to prevent progression to permanent disfiguring skin changes.**

Methods: **The medical literature was reviewed on the pathophysiology, diagnosis, and treatment of rosacea. MEDLINE was searched using the key search terms "rosacea," "rhinophyma," "metronidazole," "*Helicobacter pylori*," and "facial redness."**

Results and Conclusions: **Rosacea is easily diagnosed by physician observation, and physicians should initiate discussion of rosacea treatment with patients. Effective treatment of rosacea includes avoidance of triggers, topical and oral antibiotic therapy, both topical and oral retinoid therapy, topical vitamin C therapy, and cosmetic surgery. (J Am Board Fam Pract 2002;15:214–7.)**

As the general population ages and the baby boomers increasingly dominate clinical practice, a frequent complaint is the red face. Of the many causes of the red face, rosacea will be the diagnosis for approximately 13 million Americans.[1] Although not a life-threatening condition, rosacea produces conspicuous facial redness and blemishes that can have a deep impact on a patient's self-esteem and quality of life. Rhinophyma, the most prominent feature of advanced rosacea, is often mistakenly associated with alcoholism, as caricatured by W.C. Fields, further stigmatizing rosacea patients. A survey by the National Rosacea Society reported that 75% of rosacea patients felt low self-esteem, 70% felt embarrassment, 69% report frustration, 56% felt that they had been "robbed of pleasure or happiness," 60% felt the disorder negatively affected their professional interactions, and 57% believed that it adversely affected their social lives.[2] Much of this suffering is unnecessary, however, because rosacea is a condition that can be easily diagnosed and effectively treated in most patients.

Methods

We undertook a literature review on the pathophysiology, diagnosis, and treatment of rosacea using MEDLINE. Key search terms included "rosacea," "rhinophyma," "metronidazole," "*Helicobacter pylori*," and "facial redness."

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Diagnosis

Rosacea develops gradually. Many patients, unaware that they suffer from a treatable skin condition, assume that the intermittent facial flushing, papules, and pustules are adult acne, sun or wind burn, or normal effects of aging. Correct diagnosis and early treatment of rosacea are important because, if left untreated, rosacea can progress to irreversible disfigurement and vision loss.[3] Rosacea is a vascular disorder of distinct, predictable symptoms that follows a remarkably homogenous clinical course. Rosacea generally involves the cheeks, nose, chin, and forehead, with a predilection for the nose in men.[4]

There are four acknowledged general stages of rosacea (Table 1).[4] Stage I can be described as pre-rosacea. This stage is characterized by frequent blushing, especially in those who have a family history of rosacea. Blushing as a symptom of rosacea can start in childhood, although the typical age of onset for rosacea is 30 to 60 years.[5] There might be increased frequency of facial flushing or complaints of burning, redness, and stinging when using common skin care products or antiacne therapies. The second stage of rosacea is vascular. At this point in the disease progression, transitory erythema of midfacial areas, as well as slight telangiectasias, become apparent.[4] In the third stage of

Table 1. Rosacea Staging.

Stage	Symptoms and Signs
I	Pre-rosacea
	Frequent blushing
	Easy irritation and erythema of facial skin
II	Vascular stage
	Transitory erythema of midfacial areas
	Early telangiectasias
III	Deeper facial erythema
	Increased telangiectasias
	Papule and pustule formation
IV	Tissue hyperplasia
	Rhinophyma
	Possible ocular inflammation

Table 2. Brief Differential Diagnosis of Rosacea.

Flushing, autonomic mediated
Exercise
Spicy food
Emotions
Horner syndrome
Rosacea
Atopic dermatitis
Seborrheic dermatitis
Systemic lupus erythematosus
Dermatomyositis
Acne vulgaris and steroid-induced acne
Perioral dermatitis
Physical erythema
Mechanical
Thermal
Electromagnetic
Contact and photocontact dermatitis
Medications
Sarcoidosis

Adapted from Murray.[8]

rosacea, the facial redness becomes deeper and permanent. Telangiectasias increase, and papules and pustules begin to develop. During this stage, ocular changes, such as conjunctivitis and blepharitis, can develop.[6] Edema can develop in the region above the nasolabial folds. In the fourth stage, there is continued and increased skin and ocular inflammation. Ocular inflammation can progress to keratitis and result in loss of vision. Multiple telangiectasias can be found in the paranasal region. It is at this point that fibroplasia and sebaceous hyperplasia of the skin produces the nasal enlargement known as rhinophyma.[4]

Several skin conditions share some clinical features with rosacea. Acne vulgaris causes comedones, papules, pustules, and localized inflammatory nodules but not the generalized erythema, telangiectasias, and other vascular features of rosacea. Seborrheic dermatitis, perioral dermatitis, and the malar rash of lupus can all cause mild erythema, but these conditions will not produce the characteristic flushing, telangiectasias, papules, and pustules of rosacea.[1] Sarcoidosis can closely mimic rosacea by producing red papules on the face, but the disease will usually manifest itself in other organs as well. In addition, a biopsy will show sarcoid granulomas.[7] A more complete listing of the differential diagnosis appears in Table 2.

Pathophysiology

Although the exact pathogenesis of rosacea is unknown, the pathologic process is well described. The erythema of rosacea is caused by dilation of the superficial vasculature of the face.[1] It is thought that atrophy of the papillary dermis provides for easier visualization of the dermal capillaries.[9] Edema can develop as a result of the increased blood flow in the superficial vasculature. This edema might contribute to the late-stage fibroplasia and rhinophyma.[1] It has been suggested that *Helicobacter pylori* infection is a cause of rosacea. *H pylori*, originally implicated as the cause of gastric ulcers, has more recently been associated with urticaria, Henoch-Schönlein purpura, and Sjögren syndrome. In a 1999 study, however, Bamford et al[10] found there was no benefit in the eradication of *H pylori* compared with placebo in the treatment of rosacea, although both subjects and controls experienced improvement in the rosacea symptoms. Thus the role of *H pylori* in rosacea remains uncertain, and the cause of rosacea remains elusive.

Treatment

The most important first step in the treatment of rosacea is the avoidance of triggers. Triggers are both exposures and situations that can cause a flare-up of the flushing and skin changes in rosacea. Principal among these is sun exposure. Rosacea patients must be advised always to apply a nonirritating facial sun block when outdoors. Stress, through autonomic activation, can also increase the flushing. Alcohol consumption, while not a cause in

itself, can aggravate this condition through peripheral vasodilation. Spicy foods can also aggravate the symptoms of rosacea through autonomic stimulation. Finally, care must be taken to use only those facial cleansers, lotions, and cosmetics that are nonirritating, hypoallergenic, and noncomedogenic.

Rosacea should be treated at its earliest manifestations to mitigate progression to the stages of edema and irreversible fibrosis. Antibiotics have traditionally been considered the first line of therapy, although their success is considered to be primarily due to anti-inflammatory effects rather than antimicrobial ones.[4] Topical metronidazole, which is effective for stage I and stage II rosacea and avoids the toxicity of systemic treatment, is considered first-line therapy.[11] Metronidazole is available in a twice-daily application of 0.75% cream or gel and in a newer once-daily 1.0% formulation.[4] No significant difference in efficacy has been found between the once-daily 1.0% medicine and the twice-daily 0.75% medicine.[12] Sulfacetamide lotion can also be used in place of metronidazole. In certain patients, sulfacetamide might be less irritating than metronidazole.[4]

Rosacea responds well to oral antibiotics. Starting treatment with simultaneous oral and topical therapy reduces initial prominent symptoms, prevents relapse when oral therapy is discontinued, and maintains long-term control.[6] Oral therapy is generally continued until inflammatory lesions clear or for 12 weeks, whichever comes first.[12] Tetracycline is the primary oral antibiotic prescribed for rosacea therapy, at a dosage of 1.0 to 1.5 g/d divided into 2 to 4 daily doses. Minocycline at 100 mg two times a day is an acceptable alternative.[13] Doxycycline is another acceptable alternative, although the monohydrate formulation, in a dosage of 100 mg once daily, is more consistently effective and has fewer gastrointestinal side effects than the hyclate form.[13,14] Clarithromycin, 250 mg to 500 mg twice daily, has been found to be as effective as doxycycline but with a more benign side effect profile.[15]

New Therapies

Azelaic acid is a naturally occurring, dicarboxylic acid possessing antibacterial activity. It is available as a 20% cream and is generally used as an alternative treatment for acne vulgaris. In 1999 Maddin[16] compared once-daily applications of azelaic acid with topical metronidazole 0.75% cream for treatment of papulopustular rosacea. Maddin concluded that both medicines were equally effective in reducing the number of inflammatory lesions and the associated signs and symptoms of rosacea. When the study physicians' rating of the overall improvement was considered, however, the azelaic acid was considered to be considerably more effective. The patients involved in the study also preferred the azelaic acid.[16]

Topical retinoic acid has been shown to have a beneficial effect on the vascular component of rosacea.[17] The drawbacks of retinoic acid therapy include delayed onset of effectiveness, dry skin, erythema, burning, and stinging.[17] Retinaldehyde is intermediate in the natural metabolism of retinoids, between retinal and retinoic acid, and is generally well tolerated while retaining most of the therapeutic activity of retinoic acid.[17] Daily application of a 0.05% retinaldehyde cream for 6 months was found to yield positive and statistically significant outcomes in 75% of those patients undergoing treatment.[17] Specifically, improvements were found in erythema and telangiectasias, the vascular components of rosacea.

Topical vitamin C preparations have recently been studied in the reduction of the erythema of rosacea.[18] Daily use of an over-the-counter cosmetic 5.0% vitamin C (L-ascorbic acid) preparation was used in an observer-blinded and placebo-controlled study. Nine of the 12 participants experienced both objective and subjective improvement in their erythema.[18] It was suggested that free-radical production might play a role in the inflammatory reaction of rosacea, and that the antioxidant effect of L-ascorbic acid might be responsible for its effect. These promising preliminary results still need to be confirmed in larger, long-term studies.

Treatment of Advanced Disease

Recalcitrant rosacea can respond to oral isotretinoin therapy. In a recent study of 22 patients with mild to moderate rosacea, major reductions in erythema, papules, and telangiectasias were noted by the ninth week of treatment.[19] Isotretinoin reduces the size of sebaceous glands and alters keratinization. Recalcitrant cases of rosacea have been successfully treated with 0.5 mg/kg/d of isotretinoin.[12] Isotretinoin, of course, has serious side-effects,

most notably its teratogenic potential. Female patients of childbearing age must be strongly advised to use effective birth control. Stage IV of rosacea, involving irreversible fibrotic changes, such as rhinophyma, does not respond well to medical therapy. At that point, the patient should be referred for cosmetic surgery, such as cryosurgery and laser therapy.

In the aging US population, rosacea is an increasingly common disorder. Although rosacea causes only limited physical effects, the prominent visibility of these changes often yields intense psychosocial distress. Although the exact cause of rosacea is unknown, its progression, signs, and symptoms can be readily alleviated by the primary care physician.

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CONTINUING EDUCATION CREDIT

Rosacea: A Review

Brittney Culp, BA, and Noah Scheinfeld, MD

Educational Objectives

After reviewing this article, readers should be able to:

- Identify the common clinical presentations of rosacea.
- Review appropriate treatment options for rosacea, including topical, systemic, and other therapies.
- Differentiate between newer treatments for rosacea, both FDA-approved and non–FDA-approved.
- Determine the most appropriate treatment strategies for patients with rosacea.

Abstract

Rosacea is a chronic inflammatory condition of the facial skin affecting the blood vessels and pilosebaceous units. Rosacea is more common in persons of northern and western European descent with a fair complexion, but it can affect skin of any color. Although symptoms may wax and wane during the short term, rosacea can progress with time. Patients usually present with complaints of flushing and blushing and sensitive skin, and their skin may be especially irritated by topical preparations. Rosacea has a variety of triggers; however, they may be unnoticed by the patient.

Standard treatments approved by the FDA include azelaic acid, topical metronidazole, and oral tetracyclines, in particular minocycline and doxycycline. Other topical treatments include topical clindamycin, subantimicrobial-dose doxycycline, and sulfur products. Azithromycin and controlled-release minocycline are possible options for treating rosacea, but the FDA has not approved either agent for this indication.

Introduction

A common inflammatory condition, rosacea typically manifests in people with pale skin and light eyes, with a reported prevalence of between 0.5% and 10%.[1,2] It has many different clinical presentations as well as defined variants that help to dictate treatment.

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Epidemiology

Rosacea is more common in persons of northern and western European descent. As such, it is very common in the U.S. and in the European Union. Rosacea occurs less frequently in other ethnic groups. Some reports state that approximately 4% of rosacea patients are of African, Latino, or Asian descent.[3] It is estimated that from 10 to 20 million Americans have the condition. In a Swedish survey of people between 20 and 60 years of age, approximately 10% were thought to have rosacea, with a female-to-male ratio of 3:1. Rosacea is usually manifested as flushing in patients in their 20s, becomes troublesome to patients in their 30s, and may continue to progress thereafter.[4] Morbidity associated with rosacea typically occurs in the fourth and fifth decades of life.[5]

Pediatric rosacea is a poorly defined condition, and it is most likely underreported because of the tendency to characterize flushing and erythema as a "healthy glow." Pediatric patients are likely to have a family history of rosacea, and the condition may persist and progress in adulthood.[6]

Clinical Presentation and Diagnosis

Patients usually present with complaints of flushing, blushing, and sensitive skin. They may be unaware of these symptoms prior to diagnosis, but a variety of triggers, or factors that induce or exacerbate rosacea, exist (Table 1).[5,7,8]

Rosacea is manifested as erythematous flushing, blushing, telangiectasias, papules, and pustules affecting the central third of the face. In areas of long-standing disease, yellow-orange plaques (phymas) can develop, resulting from sebaceous hyperplasia, most commonly on the nose (rhinophyma).[9] The red papules, pustules, and telangiectasias appear in the same distribution, albeit it with a lower frequency, in Asians and Hispanics; however, because of the pigmentation, they may not appear as erythematous.[3] African-Americans generally do not have red papules and erythema; instead, they have the granulomatous form of rosacea.

Many experts report that rosacea can occur in areas other than the face. In erythemato-telangiectatic rosacea (ETR), one may observe macular redness of the ears, the lateral facial contours, the neck, the upper portion of the chest, and the scalp. These extrafacial manifestations in ETR are uncommon and are usually seen only in areas affected by flushing and by chronic sun damage. Acneiform lesions have been observed on the central part of the chest and on the scalp, the neck, and, occasionally, the limbs.[10]

Table 1 Triggers of Rosacea

Ingested/Iatrogenic	Environmental
Foods and drinks	***Temperature***
Cheese (except cottage)	Sauna heat
Chocolate	Overheating
Spicy food	Sun lamp
Soy sauce	Humidity
Vanilla	Hot baths
Dairy products	***Weather***
Liver	Sun
Beverages	Heat
Red wine	Strong wind
Hot drinks	Cold
Alcohol (beer, bourbon, gin, vodka)	***Emotion***
	Anger
Drugs	Stress
Niacin	Rage
Nitroglycerin	Embarrassment
Tobacco	***Activity***
Topical agents	Exercise
Topical corticosteroids	Menopause
Retinoids	Caffeine withdrawal
Cosmetics (sometimes)	Chronic cough
Acetones	Straining
Alcohol	

Data from Rohrich RJ, Griffin JR, Adams WP Jr. *Plast Reconstr Surg* 2002;110(3):860-869; quiz, 870;[1] and Scheinfeld NS. Rosacea. *Skinmed* 2006;5:191–194.[2]

For a diagnosis of rosacea, one or more of the following primary features concentrated on the convex areas of the face is required: flushing (transient erythema), nontransient erythema, papules and pustules, and telangiectasia. Secondary features include burning or stinging, edema, plaques, a dry appearance, ocular manifestations, peripheral locations, and phymatous changes. The relative abundance of other associated findings often dictates the subtype of disease (Table 2) and treatment.

Some clinicians still use staging for determining appropriate treatment of rosacea. Stages range from frequent flushing in pre-rosacea to rhinophyma, hyperplasia, and other inflammatory changes seen in Stage 3 (Table 3).

Variants of Rosacea and Differential Diagnosis

Two variants of rosacea are not captured in the four major subtypes presented in Table 2.

Rosacea fulminans, which manifests with multiple erythematous papules, pustules, nodules, and purulent discharging cysts, is a severe manifestation of rosacea. On rare occasions, this form can be associated with Crohn's disease, ulcerative colitis, colon cancer recurrence, and pregnancy.[11] It can be treated with prednisone 0.5 to 1 mg/kg, followed by oral isotretinoin (Accutane, Roche).

Histologically, granulomatous rosacea can resemble sarcoid or cutaneous tuberculosis. Particularly in people of color, granulomatous rosacea is manifested as firm, skin-colored papules. This type of rosacea is more prevalent in African-Americans and in Afro-Caribbeans than in persons of lighter skin. This form of rosacea usually presents as yellowish-brown nodules and papules in the malar, perioral, and periocular regions. FACE syndrome (*f*acial *A*fro-Caribbean *c*hildhood *e*ruption) is now considered a variant of granulomatous rosacea and is characterized by grouped papules in perinasal and perioral locations. The histological picture is similar to that of granulomatous rosacea.[3]

Several skin conditions resemble rosacea and should be

Table 2 Major Subtypes of Rosacea

Subtype	Characteristics
Erythemato-telangiectatic	• Flushing lasts more than 10 minutes • Burning or stinging associated with flushing • Persistent erythema of the central aspects of the face • Telangiectasias
Papulopustular	• Small, dome-shaped erythematous papules • Tiny surmounting pustules on the central aspects of the face • Solid facial erythema and edema • Phymatous changes
Phymatous	• Thickening of skin with irregular surface contours • Affects nose, chin, forehead, eyes, or eyelids
Ocular[45,46]	• Burning, stinging, and itching of eyes • Sensitivity to light • Foreign body sensations • Blepharitis • Conjunctivitis

Data from references 10, 13, 31, 45, and 46.

Table 3 Stages of Rosacea

Stage	Symptoms and Signs
Pre-rosacea	Frequent flushing Irritation caused by topical preparations
Stage 1	Transient facial erythema that becomes more persistent Slight telangiectasias Increased skin sensitivity
Stage 2	Persistent, spreading erythema Edema, papules, pustules Enlarged pores Ocular changes
Stage 3	Large inflammatory nodules and furuncles Tissue hyperplasia, fibroplasias Rhinophyma

Data from 5, 9, 10, 35, and 40.

considered in the clinical differential diagnosis. The most common conditions seen in clinical practice are listed in Table 4.

Treatment

As a result of the development and release of newer topical formulations, the diagnosis and treatment of rosacea have received renewed attention over the past several years.[12] However, the cure for rosacea remains elusive, and all currently used medications are for symptomatic control only. No precise treatment algorithm has become the standard of care; treatment remains empirical.[13,14]

According to a Cochrane Database Review, the quality of studies evaluating rosacea treatments has generally been poor. It is possible that topical metronidazole (e.g., MetroGel, MetroCream, Galderma) and azelaic acid (Azelex, Allergan) as well as oral metronidazole (Flagyl, Pfizer) and tetracycline (Sumycin, Par) might be effective, but there is insufficient evidence for the effectiveness of other treatments. Well-designed, double-blind, randomized clinical trials are needed to evaluate current treatments.[15]

The existing evidence for the treatment of rosacea in patients of color is also meager.[16] To treat darker skin successfully, clinicians must pay special attention to the presence or potential development of pigmentary alteration or keloids. Clinicians can provide effective care to these patients with the judicious use of widely available over-the-counter (OTC) and prescription products.

In view of the clinical and histological variation found in rosacea patients, it is no surprise that ETR and the papulopustular, phymatous, and glandular types respond to different therapies. From a practical standpoint, subtyping can guide therapeutic decisions. Certain modalities are useful in all patients, stemming from overlap among the subtypes; however, the timing of their use may vary.[16]

The current gold standard of oral medical treatment is tetracycline-type antibiotics. Newer light treatments, with intense pulsed light and long-pulsed dye lasers, seem to be effective at decreasing erythema and eliminating telangiectasias, but these modalities are expensive and usually do not permanently eliminate erythema or telangiectasias.[17] Flushing can be treated with medications that have provided some success in other studies, including beta-blockers, clonidine (Catapres, Boehringer Ingelheim), naloxone (Narcan, Endo), ondansetron (Zofran, GlaxoSmithKline), and selective serotonin reuptake inhibitors (SSRIs). However, evidence supporting many of these therapies is limited.[16]

FDA-approved topical and oral therapies are presented in Table 5; non–FDA-approved oral treatments are listed in Table 6, and non–FDA-approved topical treatments are outlined in Table 7.

Topical Therapy

FDA-Approved Topical Agents

The efficacy of topical therapy for rosacea relates primarily to the reduction in inflammatory lesions (papules, pustules), a decreased intensity of erythema, a decrease in the number and intensity of flares, and amelioration of symptoms, which may include stinging, pruritus, and burning. The list of standard topical agents used to treat rosacea includes topical

Table 4 **Differential Diagnosis of Rosacea**

Disease	Similarities	Differences
Acne vulgaris[9,12]	• Papules, pustules, erythema	• Comedones • Earlier onset • Not limited to central third of face • No telangiectasias or flushing
Steroid rosacea[41,47]	• Erythema, papules, pustules, telangiectasias • Central third of face	• Related to topical application of corticosteroids, tacrolimus (Protopic, Astellas/Fujisawa), and pimecrolimus (Elidel, Novartis)
Seborrheic dermatitis	• Blepharitis • Erythema	• Scaling, eczematous changes • Paranasal, nasolabial, extrafacial distribution
Perioral dermatitis[7,48]	• Erythema, papules	• Perioral distribution • Smaller lesions • No telangiectasia, flushing, or blushing
Contact dermatitis	• Erythema, papules, pustules • Burning, stinging	• Follows size and shape of causal agent • Scaling • Spongiosis and parakeratosis on histology
Photodermatitis	• Erythema, papules, plaques	• Seasonal • Usually extrafacial
Lupus	• Erythema	• Malar distribution • Photosensitivity

Data from references 7, 9, 12, 41, 47, and 48.

Table 5 FDA-Approved Topical and Oral Therapies for Rosacea

Topical Antibiotics	Non-antibiotics	Oral Antibiotics
Metronidazole 0.25%, 0.75%, 1% cream, gel, lotion (e.g., MetroCream, MetroGel)	Azelaic acid 15% gel (Azelex)	Doxycycline, USP (Oracea Capsules) 40 mg once daily (30-mg immediate-release and 10-mg delayed-release beads)
	Sodium sulfacetamide 10% and sulfur 5% combination, lotion, cream, pledgets, short-contact preparation, cleanser (Sulfacet)	
	Sodium sulfacetamide 10% lotion	
	Sodium sulfacetamide 10%, sulfur 5%, sunblock lotion combination	

antibiotics, such as clindamycin (Cleocin, Pfizer), erythromycin (Akne-Mycin, DTP Laboratories/Healthpoint Ltd.) and metronidazole, sulfacetamide–sulfur (Sulfacet, Sanofi-Aventis), and azelaic acid (Azelex).[12]

Some studies have indicated efficacy for a number of treatments. Topical metronidazole is more effective than placebo in clinical studies. Between-patient and within-patient trials showed clear improvement in those using azelaic acid when compared with placebo.[15] In a randomized trial comparing 15% azelaic acid and 0.75% metronidazole gel (MetroGel), azelaic acid was clinically superior in improving the inflammatory lesions and erythema associated with rosacea.[18] However, studies show a greater potential for irritation from azelaic acid 15% than from metronidazole gel 0.75%, which had significantly greater potential risk of irritation when compared with metronidazole 1% gel.[19] However, three cases of allergic contact dermatitis resulting from topical metronidazole have been reported.[20]

Other topical treatments include sulfur products, such as sodium sulfacetamide 10%/sulfur 5% combinations with or without a sun-blocking agent. These are available in lotions, creams, pledgets, short-contact preparations, and cleansers.

Table 6 Non–FDA-Approved Oral Treatment of Rosacea

Standard but Non-approved Oral Antibiotics	Useful but Less Commonly Used Oral Antibiotics	Oral Antibiotics Reported but Not in Common Clinical Use	Oral Treatment of Flushing	Non-antibiotic Oral Treatment
Tetracycline 500 mg b.i.d.	Azithromycin 250 mg t.i.w. (Zithromax)	Penicillin 2.4 million units q.d.	Oral contraceptives (Ovosiston)	Ivermectin 250 µ/kg q.w. (Stromectol)
Doxycycline 50–100 mg b.i.d.	Clarithromycin 250–500 mg b.i.d.–q.d. (Biaxin)	Erythromycin 250–500 mg b.i.d.–q.i.d. (Akne-Mycin)	Psychiatric medications • Amitriptyline 25 mg q.d. (Elavil) • Clonidine 0.1 mg q.d. (Catapres) • Pimozide (Orap)	Isotretinoin 0.15–2 mg/kg q.d. (Accutane)
Minocycline 50–100 mg b.i.d.	Doxycycline, subantimicrobial dose, 20 mg b.i.d. (Periostat)	Amoxicillin or ampicillin 100–500 mg q.d.–b.i.d.	Aspirin	Acitretin 25–50 mg q.d. (Soriatane)
Minocycline time-released 45, 90, 135 mg (Solodyn)		Metronidazole 250 mg b.i.d.–t.i.d. (MetroCream, MetroGel)	Beta blockers	Ketoconazole 400 mg q.d. x 1–4 weeks (Nizoral)
		Dapsone 50–200 mg q.d.	Ondansetron (Zofran)	Spirolactone 50 mg q.d. x 4 weeks (Aldactone)
			COX-2 inhibitors	Prednisone 1 mg/kg (for rosacea fulminans only)

b.i.d. = twice daily; COX-2 = cyclooxygenase-2; mg = milligram; q.d. = once daily; q.i.d. = four times daily; q.w. = weekly; t.i.w. = three times weekly.

Table 7 **Non–FDA-Approved Topical Treatment of Rosacea**

Topical Antibiotics	Topical Treatment Reportedly Used Effectively	Topical Treatments Theoretically Useful But Not Used Clinically
Clindamycin 1% lotion, gel, solution, pledget (Cleocin)	Azelaic acid 20% cream (Azelex)	Crotamiton 10% q.d.–t.i.d. (Eurax)
Erythromycin 2% solution, ointment, pledget (Akne-Mycin)	Permethrin cream 5% q.d.–q.w. (Nix)	Lindane 1% cream q.d.
Benzoyl peroxide 5%/ clindamycin 1% (BenzaClin, Benzamycin)	Adapalene cream, gel (Differin)	Benzoyl peroxide, gel, wash q.d.–b.i.d. (Benzac, Benzagel)
Sunscreen with dimethicone or cyclomethicone	Tacrolimus ointment q.d.–b.i.d. (Protopic)	Retinaldehyde 0.05% cream
Benzoyl peroxide 5% and erythromycin 1% combination cream, pledget	Pimecrolimus 1% Cream q.d.–b.i.d. (Elidel)	Tretinoin cream, gel (Retin-A)
	Oxymetazoline q.d. (Afrin)	Tazarotene cream, gel (Tazorac, Avage)

b.i.d. = twice daily; mg = milligram; q.d. = once daily; q.i.d. = four times daily; q.w. = weekly (every week).
Data from Arcangelo VP, ed. *Pharmacotherapeutics for Advanced Practice: A Practical Approach*. Lippincott Williams & Wilkins, 2005.

Sodium sulfacetamide 10% alone may also be used.

Non–FDA-Approved Topical Agents

When used for four to eight weeks, pimecrolimus 1% cream (Elidel, Novartis), a topical calcineurin inhibitor, was no more efficacious than the vehicle creams.[21] However, in an open-label, six-week pilot study in which patients used pimecrolimus 1% cream twice daily, nearly 50% of patients had clear skin and most showed at least modest improvement. Cutaneous adverse events, consisting of local burning, stinging, and itching occurred in fewer than 20% of patients.[22]

Symptomatic treatment with alpha-blockers has also been noteworthy. Patient using a topically administered selective alpha$_1$-agonist showed a positive clinical response in treatment-resistant ETR rosacea.[23] This was demonstrated as a durable improvement in the erythema, a marked decrease of erythematous flares, relief from stinging and burning, and an absence of adverse effects. It seems plausible that the erythema and flushing of ETR might result, at least in part, from an abnormal expression, function, distribution, or responsiveness of alpha-adrenergic receptors, probably of an alpha$_1$-receptor subtype and that the topical application of agonists selective for alpha$_1$-adrenergic receptors, such as oxymetazoline (Afrin, Schering-Plough) may be successful in treating these clinical manifestations.[23]

1-Methylnicotinamide 0.25% (MNA+) as a chloride salt might be a useful agent for treating rosacea.[24] Applied twice daily for four weeks, improvement rated as moderate to good was observed in 26 of 34 cases; however, seven patients showed no clinical response.

The presence of *Demodex folliculorum* may be important in the inflammatory reaction of rosacea. Crotamiton 10% cream (Eurax, Novartis in U.K.) or permethrin 5% cream (Nix, Warner-Lambert) may be useful, but these medications are rarely successful in eradicating the organism. Oral or topical ivermectin (Stromectol, Merck) may also be useful in such cases.[25]

Other experimental therapies include other topical antibiotics such as clindamycin and erythromycin as well as antibiotics combined with benzoyl peroxide (e.g., BenzaClin, Benzamycin, Dermik/Sanofi-Aventis). Increased strengths of azelaic acid have been used effectively, but are not yet approved by the FDA. Adapalene cream or gel (Differin, Galderma) has been used with some effectiveness as well. Treatments that should be theoretically useful based on pathogenesis of rosacea include lindane 1% cream, retinaldehyde 0.05% cream, tretinoin cream or gel (Retin-A, Ortho-Neutrogena), and tazarotene cream (Tazorac, Avage, Allergan). However, these agents have not yet been reported as useful in clinical practice for treating rosacea (Table 7).[14]

Oral Therapy

FDA-Approved Oral Agents

The cornerstone of the oral treatment of rosacea involves the use of tetracyclines. Tetracycline (Sumycin) 500 mg twice a day is an effective treatment, but when it is taken with food, its absorption may be decreased. Doxycycline (Vibramycin, Pfizer) and minocycline (Minocin, Triax/Wyeth) 50–100 mg once daily to twice daily are the most currently used oral antibiotics by dermatologists for the treatment of rosacea. A new time-released form of minocycline (Solodyn, Medicis) at doses of 45, 90, and 135 mg is indicated to treat only inflammatory lesions of non-nodular, moderate-to-severe acne vulgaris in patients 12 years of age and older, but it can be used if other treatment has failed. It is the first weight-based antibiotic oral therapy for rosacea.[26]

Controlled-release doxycycline 40 mg (Oracea, Galderma) is effective in treating inflammatory papules and pustules, but not erythema that is associated with rosacea.[27] Other reports have found this agent and dose to be a useful alternative to higher microbial doses of doxycycline.[26,28]

Non–FDA-Approved Oral Agents

Azithromycin (Zithromax, Pfizer), perhaps acting as an antioxidant, appears to be useful for treating rosacea in doses of 250 mg three times per week.[29,30] If azithromycin, which is now available as a generic brand, is competitively priced with minocycline and doxycycline, its minimal side effects, lack of drug interactions, and three-times-weekly dosing could make it a good alternative for rosacea patients.

The systemic treatment of *Helicobacter pylori* infection has been advocated as a possible therapy for rosacea. In some studies, the two conditions have been found to be associated. Eradication of *H. pylori* can be achieved using a triple-therapy regimen lasting one to two weeks consisting of omeprazole (Prilosec, AstraZeneca) and a combination of two of the following: clarithromycin (Biaxin, Abbott), metronidazole, or amoxicillin (Amoxil, GlaxoSmithKline).[31]

Although not commonly used clinically, other oral antibiotics with reported efficacy include penicillin 2.4 million units daily, erythromycin 250–500 mg two to four times daily, amoxicillin or ampicillin (Principen, Apothecon) 100–500 mg daily or twice daily, metronidazole at doses of 250 mg two to three times daily, and dapsone 50 to 200 mg once daily.

Non-antibacterial regimens can also be used. Isotretinoin has proved effective for rosacea.[16] Although effects may be delayed with isotretinoin, when compared with standard therapies, a reduction in the number of papules is evident within two weeks. The most significant results have been noted in younger patients with less severe manifestations of disease; however, isotretinoin has also been useful for treating and reducing phymatous changes.[16] Acitretin (Soriatane, Roche), ketoconazole (Nizoral, Janssen), spironolactone (Aldactone, Pfizer), and prednisone are also reported to be effective.

Oral agents reported to treat flushing include oral contraceptives, some psychoactive drugs, aspirin, beta-blockers, ondansetron, and cyclooxygenase-2 (COX-2) inhibitors. The oral contraceptives chlormadinon acetate/mestranol (Ovosiston) and the antiandrogen agent cyproterone have been suggested as being effective hormonal treatments for rosacea.

Combination Therapies

Effective treatments, including topical metronidazole and systemic antibiotics, have anti-inflammatory activity, which may actually be more important than their antimicrobial activity. For mild-to-moderate rosacea, an anti-inflammatory dose of doxycycline in combination with topical metronidazole gel 1% appears to be effective in reducing inflammatory lesion counts, and it is well tolerated.[32]

Phototherapy

Several reports have found light-based treatments to be effective for the erythema of rosacea. Multiplexed laser appears to help in reducing erythema and telangiectasia.[33] Intense pulsed light (IPL) at a wavelength of 550 to 670 nm may be effective for rosacea and solar lentigines, and it is particularly useful for ETR.[34] Both the flash lamp-pumped, long-pulse dye laser and the potassium-titanyl-phosphate laser may be used to treat facial telangiectasias.[25]

Nonmedical Therapies

Patients should be instructed about the regular use of sunscreens, the appropriate use of concealing makeup, and the need for careful follow-up of any ocular symptoms.[35] Basic skin-care regimens, including the daily use of a sunscreen, offer significant benefits (Table 8). Clinical assessments, confirmed by biophysical measurements (electrical capacitance, transepidermal water loss, and lactic acid stinging test), indicated that moisturizers contributed to the restoration of the skin barrier. Skin dryness, roughness, and desquamation were much improved, and skin sensitivity was significantly reduced. Skin properties were enhanced, and skin discomfort was relieved.[36]

Kinetin (N6-furfuryladenine) is a plant cytokinin that reportedly helps restore skin barrier function and may be beneficial for improving the signs and symptoms of rosacea. A twice-daily application of kinetin 0.1% lotion was found to be a well-tolerated moisturizing lotion choice for patients with mild-to-moderate inflammatory rosacea.[37,38]

In one trial, treatment with oral minocycline, spironolactone, and Chibixiao, a Chinese herb, was superior to minocycline and spironolactone alone.[39]

Beyond treating the symptoms of rosacea, physicians should address psychological problems and should provide patient education. Patients' concerns about their appearance and a lack of hope for effective therapy can cause psychological distress, which can be immediately alleviated when patients learn that rosacea is a recognized and controllable disorder. Patients are often concerned that others might believe that their symptoms are caused by overindulgence in alcohol or by poor personal hygiene.

Although alcohol consumption can exacerbate rosacea, symptoms also occur in people who abstain from alcohol. Patients should also be reassured that rosacea is often unrelated to poor hygiene. Education about triggers can help patients gain control over rosacea symptoms.[40]

Table 8 Guidelines for Sunscreen and Cosmetics in Rosacea Patients with Sensitive Skin and Skin Barrier Dysfunction

- Cleansers should be soap-free.
- Choose sunscreens that protect against ultraviolet A (UV-A) and UV-B light; titanium dioxide and zinc oxide are tolerated best.
- Cosmetics and sunscreens should contain protective silicones.
- Choose a light foundation that is easy to spread and can be set with powder; foundations that contain UV-A and UV-B sunscreen are encouraged.
- Avoid astringents, toners, menthols, camphor, and products that contain sodium lauryl sulfate.
- Avoid waterproof cosmetics and heavy foundations that are more difficult to apply and to remove without irritating solvents.

Data from Baxi S. *US Pharmacist* 2007;32(7):13–17;[42] and Pray JJ, Pray WS. *US Pharmacist* 2003;28(6).[43]

Duration of Therapy

Like acne, rosacea naturally waxes and wanes. However, because the damage from rosacea can be progressive (unlike acne), the continuous use of therapy has advantages. Many acne and rosacea patients can continue with an antibiotic for more than a year without adverse effects.[41] However, physicians should keep in mind the increased bacterial resistance caused by prolonged use of antibiotics. Long-term therapy with minocycline beyond six months also carries an increased risk of pigmentary deposition.[41]

Role of the Pharmacist

Patients with any form of facial eruption are often acutely embarrassed or highly apprehensive about consulting a pharmacist. Rosacea is a disfiguring condition, constantly visible to anyone with whom the individual has face-to-face interaction, and it can produce a great deal of stress, embarrassment, frustration, anger, and depression. Patients cannot often predict the duration of the condition, the degree of severity, or the likelihood of a favorable treatment outcome.

Pharmacists play a vital role in evaluating the patient. This includes obtaining a medication history, observing the number and types of lesions, referring patients to a physician if needed, helping to choose the appropriate therapeutic regimen, and counseling patients. Pharmacists should discuss the goals of treatment, realistic expectations, length of therapy, appropriate use of products, and the importance of adhering to the regimen.[42] Pharmacists can help physicians in educating patients about the causes of acne and rosacea by dispelling myths that these conditions are related to poor hygiene or eating poorly and by helping patients to identify triggers for worsening rosacea. The range of treatments for rosacea can be overwhelming to patients and physicians. Pharmacists can help patients choose appropriate products and advise them on when to consult a dermatologist.[43]

To decrease the risks of drug interactions, pharmacists maintain updated patient medication profiles, including use of herbal products, OTC medications, and natural supplements, and they monitor for "red-flag" drugs or drugs with a narrow therapeutic index. Pharmacists have a responsibility to warn patients and prescribers about drug interactions.[44]

Conclusion

When patients present with rosacea, appropriate therapeutic strategies should address the clinical features, the subtype of rosacea, and the staging or severity of lesions.[45–48] Patients with typical features of pre-rosacea and only transient symptoms may respond to OTC agents. However, the increasing abundance of primary rosacea features (e.g., flushing, nontransient erythema, papules, pustules, telangiectasias) and secondary features (e.g., burning, stinging, edema, ocular manifestations, extrafacial lesions, phymatous changes) should lead physicians and pharmacists to consider prescription therapy instead of OTC treatments.

For patients with inflammatory papules or pustules and a significant erythematous component, topical therapy may be considered. The most effective topical therapies seem to be azelaic acid and metronidazole. Health care providers should also take into account each patient's sensitivity to irritation from topical agents.

Oral antibiotics, such as doxycycline 50 mg daily or twice daily, can be used for rosacea that is refractory to topical therapies. Oral therapy should be considered for patients who have mostly inflammatory papules and pustules without significant erythema. Younger patients with less severe manifestations of disease and patients with phymatous changes may have excellent responses to isotretinoin.

Combinations of topical and oral therapy may provide satisfactory results for individuals with mild-to-moderate rosacea or for those with both inflammatory and erythematous components. The best combination therapy appears to be doxycycline and metronidazole gel 1%.

Physicians and pharmacists should use FDA-approved therapies unless the patient's condition is refractory to typical treatment.

Pharmacists should be reminded to obtain medication histories, to assess the severity of symptoms, and to consider referring patients for appropriate treatment. Pharmacists can be helpful in educating patients about realistic treatment outcomes and in counseling them about compliance and the appropriate use of prescribed therapies.

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Conflict of Interest (COI) Statement

The authors have no relationships to disclose. The article contains discussion of off-label use. The content of this article has been reviewed under Jefferson's Continuing Medical Education COI policy.